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DECLARATION

I, Dr. R.H. Walter, BSc., PhD., EurChem., CChem., MRSC., MITI., translator to Taylor & Meyer of 20 Kingsmead Road, London SW2 3JD, England, do solemnly and sincerely declare as follows:

1. That I am well acquainted with the English and German languages;
2. That the following is a true translation made by me into the English language of International Patent Application No. PCT/EP02/08729;
3. That all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true;

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Signed, this 13th day of January 2006,

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**Patent application in the name of Grünenthal GmbH, D-52078
Aachen
(in-house reference G 3068)**

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Salts of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives

The present invention relates to salts of substituted
10 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives,
to processes for their preparation, to drugs containing
these compounds and to their use for the preparation of
drugs for specific indications, especially for the
treatment of pain.

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The treatment of chronic and non-chronic pain conditions is
of great importance in medicine. There is a worldwide need
for highly effective pain therapies for the patient-
orientated and targeted treatment of chronic and non-
20 chronic pain conditions, this being understood as meaning
the successful and satisfactory treatment of pain for the
patient. This manifests itself in the large number of
scientific studies which have recently appeared in the
field of applied analgesis or fundamental research into
25 nociception.

Conventional opioids such as morphine are highly effective
in the therapy of intense to very intense pain. However,
their use is limited by the known side effects, e.g.
30 respiratory depression, vomiting, sedation, constipation
and the development of tolerance. Also, they are less
effective in cases of neuropathic or incidental pain, as
suffered by tumour patients in particular.

35 Opioids develop their analgesic effect by binding to
membrane-based receptors belonging to the family of the

so-called G protein coupled receptors. The biochemical and pharmacological characterization of subtypes of these receptors has now aroused the hope that subtype-specific opioids possess a different action/side effect profile from 5 that of e.g. morphine. Further pharmacological studies have since suggested the probable existence of several subtypes of these opioid receptors (μ_1 , μ_2 , κ_1 , κ_2 , κ_3 , δ_1 and δ_2).

10 In addition, there are other receptors and ion channels which play a substantial part in the system of the development and transmission of pain. The NMDA ion channel is of particular importance here because a substantial proportion of the communication of synapses passes through 15 it. The calcium ion exchange between a neuronal cell and its environment is controlled by this channel.

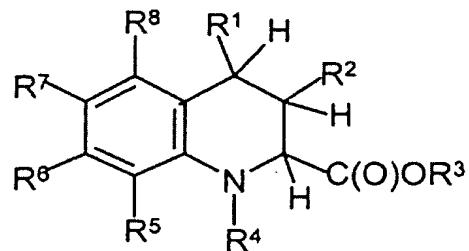
Knowledge about the physiological significance of ion channel-selective substances has been gained by the 20 development of the patch-clamp technique. The action of NMDA antagonists on the influx of calcium ions into the interior of the cell can be unambiguously demonstrated in this way. It has also been shown that these substances possess an independent antinociceptive potential (e.g. 25 ketamine). It is important here that the mechanism of action is quite different than e.g. in the case of opiates, because NMDA antagonists intervene directly in the decisive calcium balance of the cells during the transmission of pain. This affords the possibility for the first time of 30 treating neuropathic forms of pain successfully.

Various NMDA antagonists, in this case involving tetrahydroquinoline derivatives, have already been described in the articles J. Med. Chem. (1992) 35, 1954- 35 1968, J. Med. Chem. (1992) 35, 1942-1953 and Med. Chem. Res. (1991) 1, 64-73, and in patent applications EP 386

839, WO 97/12879 A1, WO 98/07704 A1 and WO 98/42673 A1. Said references, especially the patent applications, gave a large number of possible indications, including pain therapy. However, the efficacy and applicability of these 5 substances is still open to improvement, so there is a need for other substances here.

One object of the invention was to provide analgesically effective substances, especially NMDA antagonists, which 10 are suitable for pain therapy, including chronic and neuropathic pain in particular. Furthermore, these substances should exhibit a minimum of side effects, e.g. nausea, vomiting, dependence, respiratory depression or constipation.

15 Accordingly, the invention provides 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of general formula I in the form shown, or in the form of their acids or their bases, or in the form of their salts, 20 especially the physiologically acceptable salts, or in the form of their solvates, especially the hydrates, particularly in the form of their physiologically acceptable salts with cations or bases or with anions or acids, optionally in the form of their racemates or their 25 pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially the enantiomers or diastereoisomers, in any desired mixing ratio:



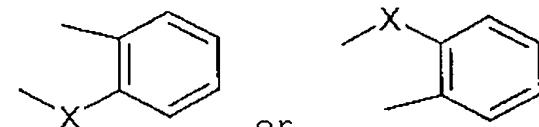
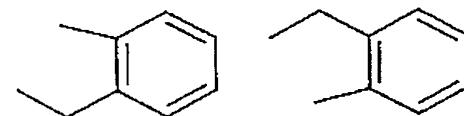
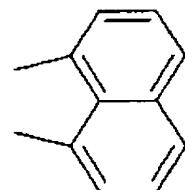
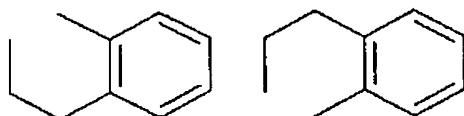
I,

in which

either

5 **R¹** and **R²** together form the following, each of which is
 monosubstituted or polysubstituted or unsubstituted:

- (CH₂)_n-, where n = 3-10,
- CH=CH-CH₂-, -CH₂-CH=CH-,
- 10 -CH=CH-CH₂-CH₂-, -CH₂-CH₂-CH=CH-,
- CH₂-CH=CH-CH₂-,
- CH₂-CH=CH-CH₂-CH₂-, -CH₂-CH₂-CH=CH-CH₂-,
- CH₂-CH₂-CH=CH-CH₂-CH₂-,
- O-CH₂-CH₂-, -CH₂-CH₂-O-,
- 15 -O-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-O-,
- CH₂-O-CH₂-,
- CH₂-CH₂-O-CH₂-, -CH₂-O-CH₂-CH₂-,



X= O, S

\mathbf{R}^3 is selected from

5 H; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each
of which is branched or unbranched and monosubstituted
or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl
which is saturated or unsaturated and monosubstituted
or polysubstituted or unsubstituted, or a
10 corresponding heterocycle in which at least one ring C
atom is replaced by N, S or O; alkylaryl or
alkylheteroaryl, each of which is monosubstituted or
polysubstituted or unsubstituted; and aryl or
heteroaryl, each of which is monosubstituted or
15 polysubstituted or unsubstituted;

naphthyl or 2-naphthyl, 2-, 3- or 4-pyridyl or thiazolyl;

SR¹⁰, where R¹⁰ is selected from

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aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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C(O)NR¹¹R¹², C(O)NR¹¹NR¹²R¹³, C(NR¹¹)NR¹²R¹³, C(S)NR¹¹R¹² or C(S)NR¹¹NR¹²R¹³, where R¹¹, R¹² and R¹³ independently of one another are selected from

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H; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding

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heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

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H; F; Cl; Br; I; CN; NO₂; and C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted;

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\mathbb{R}^4 is selected from

5 R^{4a} or ZR^{4a}, where Z = C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and R^{4a} is selected from

10 each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; and aryl or 15 heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

25 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted, especially phenethyl, 1-adamantyl, 2-adamantyl, 1-

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OR¹⁴, OC(O)R¹⁴, OC(S)R¹⁴, C(O)R¹⁴, C(O)OR¹⁴, C(S)R¹⁴, C(S)OR¹⁴, SR¹⁴, S(O)R¹⁴ or S(O₂)R¹⁴, where R¹⁴ is selected from

5 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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20 NR¹⁵R¹⁶, NR¹⁵C(O)R¹⁶, C(NR¹⁵)NR¹⁶R¹⁷, NR¹⁵C(S)R¹⁶, C(S)NR¹⁵R¹⁶, C(S)NR¹⁵NR¹⁶R¹⁷ or S(O₂)NR¹⁵R¹⁶, where R¹⁵, R¹⁶ and R¹⁷ independently of one another are selected from

25 H; O; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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or

5 R^{15} and R^{16} or R^{16} and R^{17} together form a C_3 - C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; or

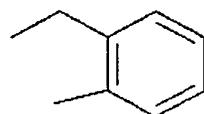
10 R^5 and R^6 , R^6 and R^7 or R^7 and R^8 together form

$=CR^{18}-CH=CH-CH=$ or $=CH-CR^{18}=CH-CH=$, where R^{18} is selected from

15 H; F; Cl; Br; I; OH; and C_1 - C_{10} -alkyl, C_2 - C_{10} -alkenyl or C_2 - C_{10} -alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted,

20 with the proviso that

if R^1 and R^2 together form $-CH=CH-CH_2-$ or



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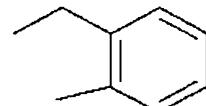
and R^3 is $(-)$ -*p*-menthan-3-ol, especially menthol or borneol, $R^7 \neq$ Cl and R^5 , R^6 and $R^8 \neq$ H simultaneously,

30 if R^1 and R^2 together form $-CH=CH-CH_2-$ and R^3 is CH_3 , $R^7 \neq$ H, Cl or OCH_3 and R^5 , R^6 and $R^8 \neq$ H simultaneously,

if R^{1b} and R^{2a} together form $-CH=CH-CH_2-$ and R^3 is H, $R^7 \neq OCH_3$ or $C(O)NH_2$ and R^5 , R^6 and $R^8 \neq$ H, R^5 and $R^7 \neq$ CH_3 and R^6 and $R^8 \neq$ H, or $R^5 \neq OCH_3$ and R^6 , R^7 and $R^8 \neq$ H

simultaneously, or

if R^{1b} and R^{2a} together form



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or -O-CH₂-CH₂- and R³ is C₂H₅, R⁷ ≠ H, Cl, CH₃, OCH₃ or NO₂ and R⁵, R⁶ and R⁸ ≠ H, or R⁵ ≠ NO₂ and R⁶, R⁷ and R⁸ ≠ H simultaneously;

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or

R¹ is selected from

15 C₁-C₁₀-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one 20 ring C atom is replaced by S, O or N; alkylaryl which is monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

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OR¹⁹, SR¹⁹ or SO₂R¹⁹, where R¹⁹ is selected from

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C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; and

alkylaryl, aryl, alkylheteroaryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

5 \mathbf{R}^2 is selected from

10 H; $\text{C}_1\text{-C}_{10}$ -alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and phenyl which is monosubstituted or polysubstituted or unsubstituted, where if \mathbf{R}^2 is phenyl, \mathbf{R}^1 must be aryl, O-aryl or S-aryl;

\mathbf{R}^3 is selected from

15 H; $\text{C}_1\text{-C}_{18}$ -alkyl, $\text{C}_2\text{-C}_{18}$ -alkenyl or $\text{C}_2\text{-C}_{18}$ -alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; $\text{C}_3\text{-C}_8$ -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a 20 corresponding heterocycle in which at least one ring C atom is replaced by N, S or O; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or 25 polysubstituted or unsubstituted;

\mathbf{R}^4 is selected from

30 \mathbf{R}^{4a} or $\mathbf{Z}\mathbf{R}^{4a}$, where $\mathbf{Z} = \text{C}_1\text{-C}_6$ -alkyl, $\text{C}_2\text{-C}_6$ -alkenyl or $\text{C}_2\text{-C}_6$ -alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and \mathbf{R}^{4a} is selected from

35 H; $\text{C}_1\text{-C}_{12}$ -alkyl, $\text{C}_2\text{-C}_{12}$ -alkenyl or $\text{C}_2\text{-C}_{12}$ -alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or

unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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C(O)R⁹, C(O)OR⁹, C(S)R⁹, C(S)OR⁹ or S(O₂)R⁹, where R⁹ is selected from

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H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted, especially phenethyl, 1-adamantyl, 2-adamantyl, 1-naphthyl or 2-naphthyl, 2-, 3- or 4-pyridyl or thiazolyl;

SR¹⁰, where R¹⁰ is selected from

aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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C(O)NR¹¹R¹², C(O)NR¹¹NR¹²R¹³, C(NR¹¹)NR¹²R¹³,

$C(S)NR^{11}R^{12}$ or $C(S)NR^{11}NR^{12}R^{13}$, where R^{11} , R^{12} and R^{13} independently of one another are selected from

5 H; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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R⁵, R⁶, R⁷ and R⁸ independently of one another are selected
20 from

H; F; Cl; Br; I; CN; NO₂; and C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted;

OR¹⁴, OC(O)R¹⁴, OC(S)R¹⁴, C(O)R¹⁴, C(O)OR¹⁴, C(S)R¹⁴, C(S)OR¹⁴, SR¹⁴, S(O)R¹⁴ or S(O₂)R¹⁴, where R¹⁴ is selected from

30 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl,
each of which is branched or unbranched and
monosubstituted or polysubstituted or
unsubstituted; C₃-C₈-cycloalkyl which is saturated
35 or unsaturated and monosubstituted or
polysubstituted or unsubstituted, or a

corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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10 $NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $C(NR^{15})NR^{16}R^{17}$, $NR^{15}C(S)R^{16}$,
 $C(S)NR^{15}R^{16}$, $C(S)NR^{15}NR^{16}R^{17}$ or $S(O_2)NR^{15}R^{16}$, where R^{15} , R^{16} and R^{17} independently of one another are selected from

15 H; O; C_1-C_{18} -alkyl, C_2-C_{18} -alkenyl or C_2-C_{18} -alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C_3-C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

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25

or

30 R^{15} and R^{16} or R^{16} and R^{17} together form a C_3-C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one C atom is replaced by S, O or N; or

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R^5 and R^6 , R^6 and R^7 or R^7 and R^8 together form

=CR¹⁸-CH=CH-CH= or =CH-CR¹⁸=CH-CH=, where R¹⁸ is selected from

5 H; F; Cl; Br; I; OH; and C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted,

10 with the proviso that

15 if R⁴, R⁶, R⁷ and R⁸ = H,

• R¹ ≠ CH₃, R³ ≠ H or CH₃ and R² and R⁵ ≠ H simultaneously;

or

• R¹ ≠ unsubstituted phenyl, R³ ≠ C₂H₅ and R² and R⁵ ≠ H

15 simultaneously;

if R⁴, R⁵, R⁶ and R⁸ = H,

• R¹ ≠ S-phenyl, R² ≠ H, R⁷ ≠ Cl and R³ ≠ CH₃ simultaneously;

or

20 • R¹ ≠ S-2-pyridinyl, R² ≠ CH₃, R⁷ ≠ OCH₃ and R³ ≠ -CH₃-CH=CH₂ simultaneously; or

if R², R⁴, R⁵ and R⁷ = H and R⁶ and R⁸ = Cl,

• R¹ ≠ dioxalane and R³ ≠ -CH₂-CH₂-OH simultaneously.

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The 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives or their salts according to the invention exhibit a pronounced analgesic action and are also NMDA antagonists which selectively attack at the glycine binding site, and.

30 In terms of the present invention, alkyl or cycloalkyl radicals are understood as meaning saturated and unsaturated (but not aromatic), branched, unbranched and cyclic hydrocarbons which can be unsubstituted or monosubstituted or polysubstituted. C₁₋₂-alkyl is C₁- or

C₂-alkyl, C₁₋₃-alkyl is C1-, C2- or C3-alkyl, C₁₋₄-alkyl is C1-, C2-, C3- or C4-alkyl, C₁₋₅-alkyl is C1-, C2-, C3-, C4- or C5-alkyl, C₁₋₆-alkyl is C1-, C2-, C3-, C4-, C5- or C6-alkyl, C₁₋₇-alkyl is C1-, C2-, C3-, C4-, C5-, C6- or C7-alkyl, C₁₋₈-alkyl is C1-, C2-, C3-, C4-, C5-, C6-, C7- or C8-alkyl, C₁₋₁₀-alkyl is C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9- or C10-alkyl and C₁₋₁₈-alkyl is C1-, C2-, C3-, C4-, C5-, C6-, C7-, C8-, C9-, C10-, C11-, C12-, C13-, C14-, C15-, C16-, C17- or C18-alkyl. Also, C₃₋₄-cycloalkyl is C3- or C4-cycloalkyl, C₃₋₅-cycloalkyl is C3-, C4- or C5-cycloalkyl, C₃₋₆-cycloalkyl is C3-, C4-, C5- or C6-cycloalkyl, C₃₋₇-cycloalkyl is C3-, C4-, C5-, C6- or C7-cycloalkyl, C₃₋₈-cycloalkyl is C3-, C4-, C5-, C6-, C7- or C8-cycloalkyl, C₄₋₅-cycloalkyl is C4- or C5-cycloalkyl, C₄₋₆-cycloalkyl is C4-, C5- or C6-cycloalkyl, C₄₋₇-cycloalkyl is C4-, C5-, C6- or C7-cycloalkyl, C₅₋₆-cycloalkyl is C5- or C6-cycloalkyl and C₅₋₇-cycloalkyl is C5-, C6- or C7-cycloalkyl. 'Cycloalkyl' also embraces saturated cycloalkyls in which one or 2 carbon atoms are replaced by the heteroatom S, N or O. However, 'cycloalkyl' also includes especially monounsaturated or polyunsaturated and preferably monounsaturated cycloalkyls without a heteroatom in the ring as long as the cycloalkyl is not an aromatic system. The alkyl or cycloalkyl radicals are preferably methyl, ethyl, vinyl (ethenyl), propyl, allyl (2-propenyl), 1-propynyl, methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, hexyl, 1-methylpentyl, cyclopropyl, 2-methylcyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl or cyclooctyl, but also adamantyl, CHF₂, CF₃ or CH₂OH, as well as pyrazolinone, oxopyrazolinone, 1,4-dioxane or dioxolane.

35 In the context of alkyl and cycloalkyl, 'substituted' in terms of the present invention is understood as meaning the

substitution of a hydrogen radical by F, Cl, Br, I, NH₂, SH or OH, 'polysubstituted' radicals being understood as meaning that the substitution takes place both on different atoms and on the same atoms several times with the same or 5 different substituents, for example three times on the same C atom, as in the case of CF₃, or at different sites, as in the case of -CH(OH)-CH=CH-CHCl₂. Particularly preferred substituents here are F, Cl and OH.

10 ' (CH₂)₃₋₆' is understood as meaning -CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-CH₂-CH₂-, '(CH₂)₁₋₄' is understood as meaning -CH₂-, -CH₂-CH₂-, -CH₂-CH₂-CH₂- and -CH₂-CH₂-CH₂-CH₂-, etc.

15 Aryl radicals are understood as meaning ring systems having at least one aromatic ring, but without heteroatoms in only one of the rings. Examples are phenyl, naphthyl, fluoroanthenyl, fluorenly, tetrailinyl or indanyl radicals, especially 9H-fluorenly or anthracenyl radicals, which can 20 be unsubstituted or monosubstituted or polysubstituted.

Heteroaryl radicals are understood as meaning heterocyclic ring systems having at least one unsaturated ring which contain one or more heteroatoms from the group comprising 25 nitrogen, oxygen and/or sulfur, and which can also be monosubstituted or polysubstituted. Examples of the heteroaryl group which may be mentioned are furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, pyrimidine, pyrazine, quinoline, isoquinoline, phthalazine, 30 benzo-1,2,5-thiadiazole, benzothiazole, indole, benzotriazole, benzodioxolane, benzodioxane, carbazole, indole and quinazoline.

In the context of aryl and heteroaryl, substituted is 35 understood as meaning the substitution of the aryl or heteroaryl with R²², OR²², a halogen, preferably F and/or Cl,

a CF₃, a CN, an NO₂, an NR²³R²⁴, a C₁₋₆-alkyl (saturated), a C₁₋₆-alkoxy, a C₃₋₈-cycloalkoxy, a C₃₋₈-cycloalkyl or a C₂₋₆-alkylene.

5 The radical R²² is H, a C₁₋₁₀-alkyl radical, preferably a C₁₋₆-alkyl radical, an aryl or heteroaryl radical or an aryl or heteroaryl radical bonded via a C₁₋₃-alkylene group, it being impossible for these aryl and heteroaryl radicals to themselves be substituted by aryl or heteroaryl radicals,

10 the radicals R²³ and R²⁴, which are identical or different, are H, a C₁₋₁₀-alkyl radical, preferably a C₁₋₆-alkyl radical, an aryl or heteroaryl radical or an aryl or heteroaryl radical bonded via a C₁₋₃-alkylene group, it being impossible for these aryl and heteroaryl radicals to themselves be substituted by aryl or heteroaryl radicals,

15 or the radicals R²³ and R²⁴ together are CH₂CH₂OCH₂CH₂, CH₂CH₂NR²⁵CH₂CH₂ or (CH₂)₃₋₆, and

20 the radical R²⁵ is H, a C₁₋₁₀-alkyl radical, preferably a C₁₋₆-alkyl radical, an aryl or heteroaryl radical or an aryl or heteroaryl radical bonded via a C₁₋₃-alkylene group, it being impossible for these aryl and heteroaryl radicals to themselves be substituted by aryl or heteroaryl radicals.

25 'Salt' is understood as meaning any form of the active ingredient according to the invention in which it takes on an ionic (here usually anionic) form, or is charged, and is coupled with a counterion (here usually a cation) or is in solution. This is understood as including complexes of the active ingredient with other molecules and ions, especially complexes that are complexed via ionic interactions.

30 35 In terms of the present invention, 'physiologically acceptable salts with cations or bases' are understood as

meaning salts of at least one of the compounds according to the invention - usually a (deprotonated) acid - as an anion with at least one, preferably inorganic cation, which are physiologically acceptable, especially when used in humans and/or mammals. Particularly preferred salts are those of alkali metals and alkaline earth metals and also NH_4^+ , but very particularly preferred salts are monosodium or disodium, monopotassium or dipotassium, magnesium or calcium salts.

10

In terms of the present invention, 'physiologically acceptable salts with anions or acids' are understood as meaning salts of at least one of the compounds according to the invention - usually protonated, e.g. on the nitrogen - as a cation with at least one anion, which are physiologically acceptable, especially when used in humans and/or mammals. In terms of the present invention, this is understood in particular as meaning the salts formed with physiologically acceptable acids, i.e. salts of the active ingredient in question with inorganic or organic acids, which are physiologically acceptable, especially when used in humans and/or mammals. Examples of physiologically acceptable salts of specific acids are salts of hydrochloric acid, hydrobromic acid, sulfuric acid, methanesulfonic acid, formic acid, acetic acid, oxalic acid, succinic acid, tartaric acid, mandelic acid, fumaric acid, lactic acid, citric acid, glutamic acid, 1,1-dioxo-1,2-dihydro-1b6-benzo[d]isothiazol-3-one (saccharinic acid), monomethylsebacic acid, 5-oxoproline, hexane-1-sulfonic acid, nicotinic acid, 2-, 3- or 4-aminobenzoic acid, 2,4,6-trimethylbenzoic acid, a-lipoic acid, acetylglycine, acetylsalicylic acid, hippuric acid and/or aspartic acid. The hydrochloride salt is particularly preferred.

35 In terms of the present invention, preferred derivatives are the substituted 1,2,3,4-tetrahydroquinoline-2-

carboxylic acid derivatives of formula I in the form of their physiologically acceptable salts with cations or bases. These salts are called 'salts according to the invention' or 'salts according to the invention of 5 substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I' in the description which follows. However, 'salts according to the invention' or 'salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of 10 formula I' are not necessarily restricted to physiologically acceptable salts of the substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I with cations or bases, but can optionally also include selected free bases or free acids or 15 physiologically acceptable salts with anions or acids.

One particularly preferred subject of the patent application consists of salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid 20 derivatives of formula I in which R⁴ is selected from

H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each 25 of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted; and

C(O)R⁹, where R⁹ is selected from 30
H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted; and aryl or 35

heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted, especially phenethyl, 1-adamantyl, 2-adamantyl, 1-naphthyl or 2-naphthyl, 2-, 3- or 4-pyridyl or thiazolyl.

5

Particularly preferred salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I are those in which R⁴ is selected from

10

H; C₁-C₁₀-alkyl which is unsubstituted or monosubstituted or polysubstituted; and phenyl which is unsubstituted or monosubstituted or polysubstituted, preferably H, CH₃ or C₂H₅ and especially H.

15

One preferred subject of the patent application consists of salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I in which R³ is selected from

20

H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by N or O; alkylaryl which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted.

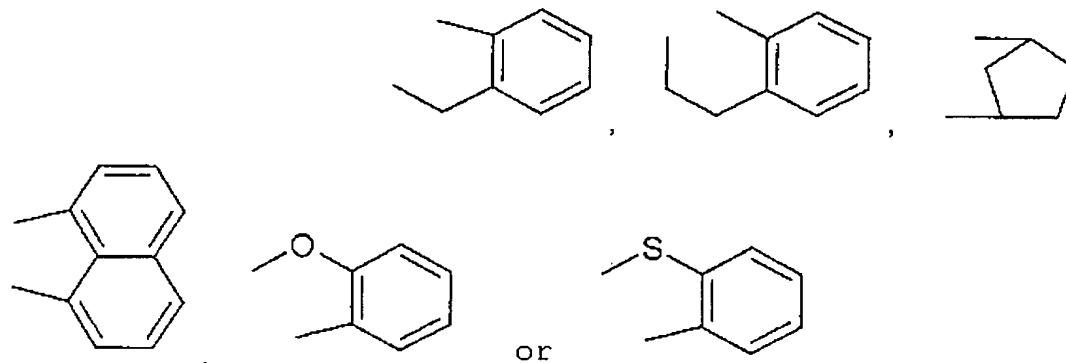
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Particularly preferred salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I are those in which R³ is selected from

30

5 H; C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and phenyl, benzyl or phenethyl which is monosubstituted or polysubstituted or unsubstituted, preferably H, CH₃ or C₂H₅ and especially H.

Particularly preferred salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid 10 derivatives of formula I are those in which R¹ and R² together form -O-CH₂-CH₂-, (-CH₂-)_n where n = 3-6, preferably 3 or 6, -CH=CH-CH₂-, -CH=CH-CH₂-CH₂-,



15 preferably -CH=CH-CH₂- or -CH=CH-CH₂-CH₂- and especially -CH=CH-CH₂-.

Another preferred subject consists of salts according to 20 the invention of substituted 1,2,3,4-tetraquinoline-2-carboxylic acid derivatives of formula I in which R¹ is selected from

25 phenyl, naphthyl or anthracenyl which is unsubstituted or monosubstituted or polysubstituted; and OR¹⁹ or SR¹⁹, where R¹⁹ is selected from

C₁-C₆-alkyl which is branched or unbranched and monosubstituted or polysubstituted or

unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

5

preferably anthracenyl, naphthyl or, in particular, phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from

10

F; Cl; Br; I; methoxy; ethoxy; propoxy; methyl; ethyl; propyl (n-propyl, i-propyl); butyl (n-butyl, i-butyl, t-butyl); carboxyl; nitro; benzyloxy; phenyl; hydroxyl; phenoxy; trifluoromethyl; dioxolyl and SCH₃;

15

or OR¹⁹ or SR¹⁹, where R¹⁹ is selected from

20

C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

25

especially unsubstituted phenyl, naphthyl and anthracenyl, O-hydroxyethyl, ethoxynaphthyl, 4-hydroxy-3-methoxyphenyl, 4-propoxyphenyl, 2,3,4-trimethylphenyl, 2,4,5-trimethoxyphenyl, SCH₃, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2,6-dichlorophenyl, 4-carboxyphenyl, 3-nitrophenyl, 2,4,6-trimethylphenyl, 2,5-dimethylphenyl, 3,4-dimethoxyphenyl, 4-benzyloxy-3-methoxyphenyl, 3-

30

35

Another preferred subject of the patent application
consists of salts according to the invention of substituted
1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives
15 of formula I in which R² is selected from

20 H; C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and phenyl which is monosubstituted or polysubstituted or unsubstituted, preferably H, unsubstituted phenyl, 4-methoxyphenyl or CH₃ and especially H.

25 One preferred subject of the patent application consists of salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I in which R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

30 H; F; Cl; Br; I; CN; NO₂; and C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted;

H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and

NR¹⁵R¹⁶ or NR¹⁵C(O)R¹⁶, R¹⁵ and R¹⁶ independently of one another being selected from

H; O; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted.

Particularly preferred salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I are those in which R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

H; F; Cl; Br; I; CN; NO₂; and C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted;

OR¹⁴, C(O)R¹⁴, C(O)OR¹⁴ or SR¹⁴, R¹⁴ being selected from

H; C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or

unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted; preferably, R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

5

H; F; Cl; Br; I; CN; and C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted;

10

OR¹⁴ or SR¹⁴, R¹⁴ being selected from

15

C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

in particular, R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

20

H; F; Cl; Br; I; CN; CH₃; CF₃; t-butyl; i-butyl; -OCH₃; -OCF₃; -SCH₃ and -O-phenyl.

25

Very particularly preferred salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I are those in which

R⁵, R⁶ and R⁸ are H and R⁷ is Cl, or R⁵ and R⁷ are H and R⁶ and R⁸ are Cl.

30

Particularly preferred subjects consist of the salts according to the invention of the following substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives:

7,9-dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-

35 quinoline-4-carboxylic acid,

8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid,

6-chloro-7-trifluoromethyl-4-(2,4,6-trimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

4-(2-hydroxyethoxy)-6-trifluoromethoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

6-iodo-4-(4-methoxyphenyl)-3-methyl-1,2,3,4-

10 tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

15 5,7-dichloro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-p-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

20

5,7-dichloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(2-fluorophenyl)-1,2,3,4-

25 tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(3-fluorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

30 5,7-dichloro-4-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(2-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

35

5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-

tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(3-bromophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

5,7-dichloro-4-(4-bromophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

7,8-dichloro-4-(2-chlorophenyl)-1,2,3,4-

10 tetrahydroquinoline-2-carboxylic acid,

6-cyano-4-(2,3,4-trimethoxyphenyl)-1,2,3,4-

tetrahydroquinoline-2-carboxylic acid,

15 6,8,9-trichloro-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]-quinoline-4-carboxylic acid,

8-methoxy-4-(4-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

20

5,6,8-trichloro-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(3,4-dimethoxyphenyl)-8-ido-1,2,3,4-tetrahydroquinoline-

25 2-carboxylic acid,

6-ido-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

30 4-(4-ethoxy-3-methoxyphenyl)-6-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(2-ethoxynaphthalen-1-yl)-6-ido-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

35

8-chloro-4-(4-propoxypyhenyl)-1,2,3,4-tetrahydroquinoline-2-

carboxylic acid,

4-(2,4-dimethoxy-3-methylphenyl)-6-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

4-anthracen-9-yl-6-chloro-8-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

6-sec-butyl-4-naphthalen-1-yl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(4-hydroxyphenyl)-3-methyl-8-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

15 8-chloro-6-fluoro-4-naphthalen-2-yl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(4-methoxyphenyl)-3-methyl-6-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

20

6-chloro-8-fluoro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

8-chloro-6-fluoro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(4-bromophenyl)-6-chloro-8-fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

30 7,8-dichloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

6-chloro-4-(4-chlorophenyl)-7-trifluoromethyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

35

4-(2-chlorophenyl)-6-cyano-1,2,3,4-tetrahydroquinoline-2-

carboxylic acid,

6-bromo-8-chloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

6-bromo-4-(2-bromophenyl)-8-chloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(4-hydroxy-3-methoxyphenyl)-3-methyl-6-methylsulfanyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

6-cyano-3,4-bis(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

15 5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(3-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

20

5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

1,3-dichloro-5,6,6a,7,8,12b-hexahydrobenzo[k]-phenanthridine-6-carboxylic acid,

1,3-dichloro-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]-quinoline-6-carboxylic acid,

30 5,7-dichloro-4-(3,5-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid and

7,9-dichloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]-quinoline-4-carboxylic acid,

35

particular preference being given to sodium 7,9-

5 dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-4-carboxylate or sodium 7,9-dichloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline-4-carboxylate, especially sodium 7,9-dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylate.

Particularly preferred salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I are the alkali metal salts, 10 preferably the sodium or potassium salts and especially the sodium salts.

15 The invention also provides processes for the preparation of salts according to the invention of a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative.

Various processes for the preparation of tetrahydroquinolines are described in the literature:

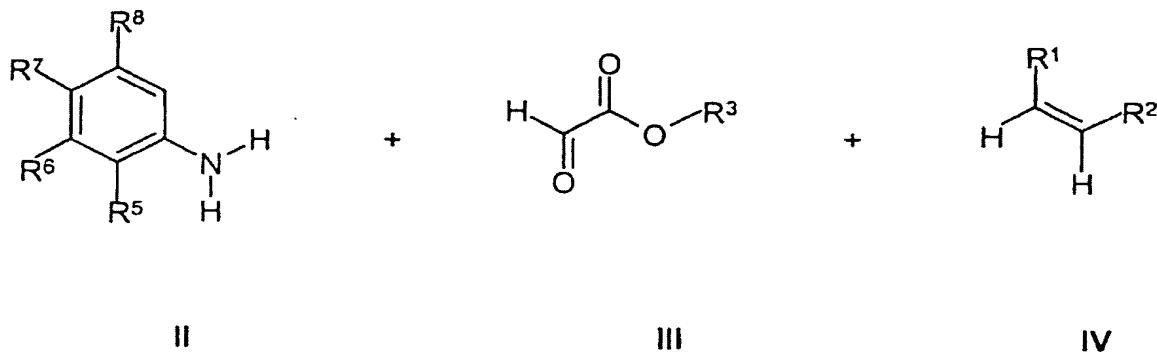
- a solid phase preparation (WO 98/34111),
- 20 • multistage procedures (WO 98/42673; Bioorganic and Medicinal Chemistry Letters, vol. 2, p. 371, 1992; Journal of Heterocyclic Chemistry, vol. 25, p. 1831, 1988; Journal of the Chemical Society, Perkin Transactions I (1989), page 2245) or
- 25 • a Lewis acid-catalyzed "one-pot" process (Journal of the Chemical Society, Chemical Communications, 1999, p. 651; Journal of the American Chemical Society, vol. 118, p. 8977, 1996).

30 However, all these processes clearly have some disadvantages.

35 In contrast to these processes, the so-called basic process described here is a process mediated by trifluoroacetic acid - preferably a "one-pot" process - in which one aromatic amine component, one aldehyde component and one

electron-rich olefin component are reacted with one another.

In the basic process, substituted 1,2,3,4-
 5 tetrahydroquinoline-2-carboxylic acid derivatives of
 formula I in which R^4 = H, the other radicals having one of
 the meanings already mentioned, are prepared first.
 Anilines of formula II, in which R^5 , R^6 , R^7 and R^8 each
 independently of one another have one of the meanings
 10 already indicated or are provided with a protecting group,



glyoxalic acid esters or optionally glyoxalic acid of
 15 formula III and olefins of formula IV, in which R^1 , R^2 and
 R^3 each independently of one another have one of the
 meanings already indicated or are provided with a
 protecting group, are reacted with trifluoroacetic acid at
 between 0°C and 100°C. The reaction time is preferably
 20 0.25 - 12 h and particularly preferably at most 2 h, the
 reaction is carried out preferably at a temperature of
 between 20 and 40°C and particularly preferably at room
 temperature, and/or the reaction is a one-pot reaction.
 When this basic process has ended, any existing ester
 25 groups can be saponified and/or the product formed in the
 basic process can optionally be brought into contact with a
 strong base, which may already contain the desired cation,
 in order to form a salt.

One decisive advantage of the process according to the invention is that it produces the desired systems according to a domino reaction (imine formation and subsequent aza Diels-Alder reaction) with very high selectivities coupled 5 with good yields.

Without having to carry out a linking or cleaving step as in the case of the solid phase preparation, and also without purification of the intermediates as in the case of 10 the solution chemistry described, the process according to the invention is distinguished not only by its ease of implementation but also by its purification method. Washing several times with non-polar solvents, for example n-hexane, makes it possible for the most part to obtain the 15 products in high purity. In other cases, they can be purified by means of column chromatography. In particular, the compounds of formula I can be obtained as the pure diastereoisomers by the washing processes with non-polar solvents, for example n-hexane, or by crystallization of 20 their salts.

In general, in one advantageous embodiment of the preparative process, when the formation of a compound of formula I has ended, the compound is brought into contact 25 with a strong base, which may already contain the desired cation, and the resulting salt according to the invention is then purified.

The majority of the reactants used here, especially those 30 of formulae II, III and IV, are commercially available or can be prepared by simple synthesis steps known to those skilled in the art.

In consecutive reactions following the basic process, the 35 products formed in the basic process can be converted to consecutive products of formula I according to the

invention by a procedure known to those skilled in the art, whereby initially the hydrogen on R^4 is substituted.

Thus, when the basic reaction has ended, if the product is
5 to be a substituted 1,2,3,4-tetrahydroquinoline-2-
carboxylic acid derivative of formula I where R^4 =
alkylformyl, acyl, sulfenyl or sulfonyl, the reaction
product can be reacted with the appropriate chloroformate
or fluoroformate, acid chloride, sulfenyl chloride or
10 sulfonyl chloride in the presence of a base, preferably
triethylamine, pyridine or NaOH, in water, a dioxane/water
mixture or a THF/water mixture, at a temperature of between
0 and 20°C (J. Org. Chem., 1989, 54, 5574-5580).

15 Likewise, when the basic reaction has ended, if the product
is to be a substituted 1,2,3,4-tetrahydroquinoline-2-
carboxylic acid derivative of formula I where R^4 =
 $C(S)NR^{11}R^{12}$, the reaction product can be reacted with a
thionating reagent, preferably Lawesson's reagent (2,4-
20 bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-
dithiaphosphetane), in an organic solvent, preferably THF
or toluene, at a temperature of 30-50°C.

Alternatively, when the basic reaction has ended, if the
25 product is to be a substituted 1,2,3,4-tetrahydroquinoline-
2-carboxylic acid derivative of formula I where R^4 =
 $C(O)NR^{11}R^{12}$ or $C(S)NR^{11}R^{12}$, the reaction product can be
reacted with potassium cyanate or potassium isothiocyanate
in water at temperatures of up to 100°C, or with an organic
30 isocyanate or isothiocyanate in an alcohol, preferably
methanol, ethanol or isopropanol, at temperatures up to the
boiling point.

Again, when the basic reaction has ended, if the product is
35 to be a substituted 1,2,3,4-tetrahydroquinoline-2-
carboxylic acid derivative of formula I where R^4 =

$C(NR^{11})NR^{12}R^{13}$, the reaction product can be reacted under alkaline conditions with an O-methylisourea or S-methylisothiourea at temperatures of 20-50°C, preferably ethanolic or methanolic NaOH or KOH.

5

Yet again, when the basic reaction has ended, if the product is to be a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I where $R^4 = C(O)NR^{11}R^{12}$, the reaction product can be reacted with propanone-2-semicarbazone in water/glacial acetic acid at 30-60°C.

Likewise, when the basic reaction has ended, if the product is to be a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I where $R^4 = C(S)NR^{11}R^{12}$, the reaction product can be reacted with CS_2 and a hydrazine in water/NaOH at 30-60°C.

As the final possibility to be mentioned here, when the basic reaction has ended, if the product is to be a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I where $R^4 =$ alkyl, benzyl or phenethyl, the reaction product can be reacted with an appropriate alkylating halide, benzyl halide or phenethyl halide and a suitable base, preferably sodium hydride or potassium tert-butyrate, in a solvent, for example ethanol, at between 0 and 100°C (J. Org. Chem., 1947, 12, 760; Zh. Obshch. Khim., 1942, 12, 418).

Under many of said reaction conditions, OH, SH and NH_2 groups may possibly enter into unwanted secondary reactions. It is therefore preferable to provide them with protecting groups or, in the case of NH_2 , to replace it with NO_2 , and to cleave the protecting group, or reduce the NO_2 group, before purifying the end product. The patent application therefore also provides a modification of the

process described above wherein, in the starting compounds, at least one OH group has been replaced by an OSi(Ph)₂tert-butyl group, at least one SH group has been replaced by an S-p-methoxybenzyl group and/or at least one NH₂ group has 5 been replaced by an NO₂ group, and at least one and preferably all of the OSi(Ph)₂tert-butyl groups are cleaved with tetrabutylammonium fluoride in tetrahydrofuran, and/or at least one and preferably all of the p-methoxybenzyl groups are cleaved with a metal amine, preferably sodamine, 10 and/or at least one and preferably all of the NO₂ groups are reduced to NH₂ before the end product is purified.

Furthermore, carboxylic acid or thiocarboxylic acid groups are sometimes unstable under said reaction conditions, so 15 it is preferable to use their methyl esters in the reactions and then to saponify the product of the process with KOH solution or NaOH solution in methanol at 40°C - 60°C. The invention therefore also provides a modification of the processes described above wherein, before the end 20 product is purified, a product of the process having at least one C(O)OCH₃, OC(O)OCH₃ and/or C(S)OCH₃ group is saponified with KOH solution or NaOH solution in methanol or ethanol at 0°C - 100°C, preferably at 40°C - 60°C.

25 Therefore, it can also be favourable, for the preparation of (salts according to the invention of) substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of formula I in which R³ = H, to use for the basic process starting materials of formula III in which R³ ≠ H and is 30 preferably alkyl, especially CH₃ and C₂H₅. After the basic process and also the consecutive reactions that may follow it, the reaction product is saponified with an appropriate base, preferably NaOH (for example 6 N) or KOH, in ethanol or methanol at temperatures of between 0 and 100°C, 35 preferably of 40°C - 60°C (Organikum, 1990, p. 418).

The following procedure is used to prepare the salts, especially the physiologically acceptable salts with cations or bases:

- 5 One equivalent of a compound of formula I, preferably an imino acid or a carboxylic acid, particularly where $R^3 = H$, is suspended in a small volume of water and one equivalent of 1 N aqueous alkaline solution, for example NaOH or KOH, is added. If the solubility is poor, methanol is added
- 10 dropwise until the compound has completely dissolved. After stirring at room temperature, the solution is concentrated on a rotary evaporator and the residual solution is frozen at low temperatures in an isopropanol/dry ice mixture and freeze-dried. The salts, especially of imino acids or carboxylic acids and preferably the sodium or potassium salts, are usually obtained as colourless solids.
- 15 An alternative possibility is to prepare the potassium or sodium salts with potassium or sodium trimethylsilyl anolate (E.D. Laganis, B.L. Chenard, Tetrahedron Letters, 25, 5831-5834 (1984)). Potassium or sodium trimethylsilyl anolate is dissolved under nitrogen in an organic solvent (e.g. dichloromethane, toluene, THF) and the ester or acid is added all at once. The reaction mixture is stirred for several hours at room temperature and filtered. The usually colourless solid is washed and dried under vacuum. The potassium or sodium salts are obtained as solids.
- 25 The salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives are toxicologically safe, so they are suitable as pharmaceutical active ingredients in drugs.
- 30 The invention therefore also provides a drug containing, as the active ingredient, at least one salt according to the invention of a substituted 1,2,3,4-tetrahydroquinoline-2-

carboxylic acid derivative of formula I in the form shown, or in the form of the acid or base, or in the form of its salts, especially the physiologically acceptable salts, or in the form of its solvates, especially the hydrates,

5 particularly in the form of its physiologically acceptable salts with cations or bases or with anions or acids, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially 10 the enantiomers or diastereoisomers, in any desired mixing ratio, and optionally containing suitable additives and/or auxiliary substances and/or optionally other active ingredients.

15 The drugs according to the invention can be administered as liquid dosage forms, i.e. injection solutions, drops or juices, or as semisolid dosage forms, i.e. granules, tablets, pellets, patches, capsules, plasters or aerosols, and optionally contain, apart from at least one salt

20 according to the invention of a substituted tetrahydroquinoline derivative, excipients, fillers, solvents, diluents, colorants and/or binders, depending on the galenical form. The choice of auxiliary substances and the amounts thereof to be used depend on whether the drug 25 is to be administered orally, perorally, parenterally, intravenously, intraperitoneally, intradermally, intramuscularly, intranasally, buccally, rectally or locally, for example to infections on the skin, mucous membranes or eyes. Suitable preparations for oral

30 administration are those in the form of tablets, dragees, capsules, granules, drops, juices and syrups, and suitable preparations for parenteral, topical and inhalational administration are solutions, suspensions, readily reconstitutable dry preparations and sprays. Salts

35 according to the invention of substituted tetrahydroquinoline derivatives in a depot in dissolved form or in a plaster, optionally with the addition of skin

penetration promoters, are suitable preparations for transdermal application. Preparative forms for oral or transdermal administration can release the salts according to the invention of substituted tetrahydroquinoline derivatives in a delayed manner. The amount of active ingredient to be administered to the patient varies according to the patient's weight, the mode of administration, the indication and the severity of the disease. Conventionally, 2 to 500 mg/kg of at least one salt according to the invention of a substituted tetrahydroquinoline derivative of formula I are administered.

Preferably, the salts according to the invention of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives are used for the treatment of pain, especially chronic and neuropathic pain, as well as migraine, so the invention also provides the use of at least one salt according to the invention of a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially the enantiomers or diastereoisomers, in any desired mixing ratio, for the preparation of a drug for the treatment of pain, especially neuropathic and/or chronic pain, and/or for the treatment of migraine.

The affinity for the NMDA receptor gives rise to other areas of application since it is known that NMDA antagonists have *inter alia* a neuroprotective action and can therefore also be used satisfactorily for syndromes associated with neurodegeneration and neural damage, such as Parkinson's disease and Huntington's chorea, etc. Other indications of the NMDA antagonists according to the invention are epilepsy, glaucoma, osteoporosis,

ototoxicity, withdrawal symptoms associated with alcohol and/or drug abuse, stroke, including related cerebral ischaemia, cerebral infarction, cerebral oedema, hypoxia and anoxia, and also use for anxiolysis and in anaesthesia.

5 The invention therefore also provides the use of at least one salt according to the invention of a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or

10 diastereoisomers, or in the form of mixtures of the stereoisomers, especially the enantiomers or diastereoisomers, in any desired mixing ratio, for the preparation of a drug for the treatment/prophylaxis of epilepsy, Parkinson's disease, Huntington's chorea,

15 glaucoma, ototoxicity, withdrawal symptoms associated with alcohol and/or drug abuse, stroke, cerebral ischaemia, cerebral infarction, cerebral oedema, hypoxia and anoxia, and/or for anxiolysis and/or anaesthesia.

20 Surprisingly, it has been found that the substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives according to the invention are also very suitable for other indications and especially for the treatment of urinary incontinence, pruritus, tinnitus aurium and/or diarrhoea.

25 The patent application therefore also provides the use of at least one salt according to the invention of a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers

30 or diastereoisomers, or in the form of mixtures of the stereoisomers, especially the enantiomers or diastereoisomers, in any desired mixing ratio, for the preparation of a drug for the treatment of urinary incontinence, pruritus, tinnitus aurium and/or diarrhoea.

35

However, the compounds according to the invention are also

effective in other indications. The patent application therefore also provides the use of at least one salt according to the invention of a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially the enantiomers or diastereoisomers, in any desired mixing ratio, for the treatment/prophylaxis of schizophrenia, Alzheimer's disease, psychosis due to a raised amino acid level, AIDS-related dementia, encephalomyelitis, Tourette syndrome, perinatal asphyxia, inflammatory and allergic reactions, depression, drug and/or alcohol abuse, gastritis, diabetes, cardiovascular disease, respiratory tract disease, cough and/or mental disease.

The invention also provides a method of treating a non-human mammal or a human in need of a treatment for medically relevant symptoms, by the administration of a therapeutically effective dose of a salt according to the invention of a substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivative of formula I, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially the enantiomers or diastereoisomers, in any desired mixing ratio, or a drug according to the invention. The invention relates especially to appropriate methods for the treatment of pain, especially neuropathic and/or chronic pain, and/or for the treatment of migraine, for the treatment of urinary incontinence, pruritus, tinnitus aurium and/or diarrhoea, for the treatment/prophylaxis of epilepsy, Parkinson's disease, Huntington's chorea, glaucoma, osteoporosis, ototoxicity, withdrawal symptoms associated with alcohol and/or drug abuse, stroke, cerebral ischaemia, cerebral infarction, cerebral oedema, hypoxia and anoxia, and/or for

anxiolysis and/or anaesthesia, or for the treatment/prophylaxis of schizophrenia, Alzheimer's disease, psychosis due to a raised amino acid level, AIDS-related dementia, encephalomyelitis, Tourette syndrome, perinatal asphyxia, inflammatory and allergic reactions, depression, drug and/or alcohol abuse, gastritis, diabetes, cardiovascular disease, respiratory tract disease, cough and/or mental disease.

10 The invention is further illustrated below by means of Examples, which do not imply a limitation.

Examples

15 The Examples which follow show compounds according to the invention, their preparation and efficacy tests performed therewith.

The following information is generally applicable:

20 The chemicals and solvents used were acquired commercially from the conventional suppliers (Acros, Avocado, Aldrich, Fluka, Lancaster, Maybridge, Merck, Sigma, TCI, etc.) or synthesized.

25 In particular, some of the compounds used are synthesized as synthetic moieties by known procedures before the basic synthesis described below.

30 The thin layer chromatography tests were carried out with HPTLC precoated plates, silica gel 60 F 254, from E. Merck, Darmstadt.

The yields of the compounds prepared are not optimized.

35 The analysis was performed by ESI mass spectroscopy.

The compounds are numbered, the data in brackets corresponding in principle to the number of the assigned compound.

5

Example 0**Basic process for the preparation of the basic compounds of formula I**

10

a) One equivalent of aniline derivative and one equivalent of trifluoroacetic acid are dissolved in 6 ml/mmol of acetonitrile at room temperature, with stirring, and 1.1 equivalents of ethyl glyoxalate (50% in toluene) or 1.1 equivalents of glyoxalic acid monohydrate are then added. After ten minutes, 3 equivalents of the olefin component are added and the course of the reaction is followed by thin layer chromatography (solvent system: diethyl ether/hexane, 1:1). The reaction has ended after 2 hours (TLC check). An excess of saturated aqueous sodium hydrogencarbonate solution is added to the reaction mixture and the organic phase is extracted three times with diethyl ether. The organic phase is washed with water until the washings are neutral and dried over magnesium sulfate, the magnesium sulfate is filtered off and washed with diethyl ether, the product phase is concentrated and the product is isolated by recrystallization or silica gel chromatography. The 1,2,3,4-tetrahydroquinoline-2-carboxylic acid ester is characterized by ESI mass spectrometry.

30

b) Optional subsequent preparation of the free 1,2,3,4-tetrahydroquinoline-2-carboxylic acids

The above-described 1,2,3,4-tetrahydroquinoline-2-carboxylic acid ester (1 equivalent) is dissolved in 4 ml/mmol of ethanol, and 1.2 equivalents of 6 N aqueous

35

sodium hydroxide solution are added at room temperature, with stirring. The course of the ester saponification is followed by thin layer chromatography (solvent system: diethyl ether/hexane, 1:1) and has ended after 30 minutes 5 (TLC check). The reaction mixture is concentrated on a rotary evaporator, taken up in approx. 10 ml of water and adjusted to pH 1 with 32% HCl. The aqueous solution is extracted five times with diethyl ether, dried over magnesium sulfate and concentrated.

10

Automated process

A round-bottom screw-threaded glass tube (diameter 16 mm, length 125 mm) was provided with a stirrer and sealed with a screw cap comprising a septum. The tube was placed in a 15 stirring block thermostatted at 20°C. The following reactants were then pipetted successively into the tube:

1 ml of a solution of 0.1 M trifluoroacetic acid and 0.1 M aniline component in acetonitrile;
20 1 ml of a 0.11 M solution of the aldehyde in acetonitrile;
1 ml of a 0.3 M solution of the olefin in acetonitrile.

The reaction mixture was stirred for 10 h at 20°C in one of the stirring blocks. The reaction solution was then 25 filtered, the tube being rinsed with twice 1.5 ml of 7.5% NaHCO₃ solution.

2 ml of ethyl acetate were added to the reaction mixture on a vortex shaker and the mixture was shaken. It was 30 centrifuged briefly to form the phase boundary. This was detected optically and the organic phase was pipetted off. In the next step a further 2 ml of ethyl acetate were added to the aqueous phase, the mixture was shaken and centrifuged and the organic phase was pipetted off. The 35 combined organic phases were dried over 2.4 g of MgSO₄ (granulated). The solvent was stripped off in a vacuum

centrifuge.

The free 1,2,3,4-tetrahydroquinoline-2-carboxylic acid or the ester is characterized by ESI mass spectrometry.

5

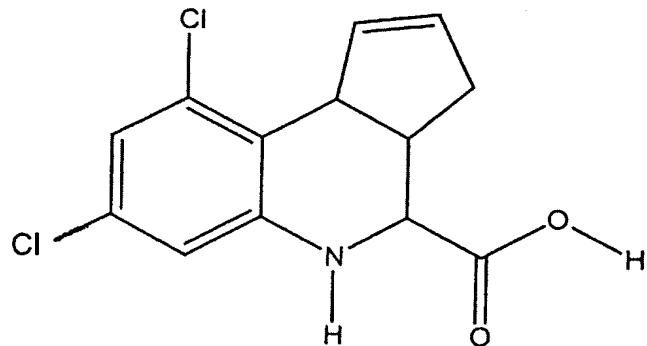
In principle, in the case of compounds where $R^3 \neq H$, both the automated process and the normal basic process can be followed by a saponification using methods known to those skilled in the art, for example with KOH solution or NaOH solution in methanol or ethanol at $0^\circ\text{C} - 100^\circ\text{C}$, preferably 10 at $40^\circ\text{C} - 60^\circ\text{C}$.

Examples 1 to ... which now follow show the preparation of the basic compounds of formula I by one of the processes of 15 Example 0, salts according to the invention of said compounds being prepared after the particular preparation described.

Example 1

20

7,9-Dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-4-carboxylic acid (**1**)



25

Compound **1** was saponified with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol. The ethanolic solution was concentrated on a rotary evaporator, the residue was taken up in water, 6 N HCl was added and the

aqueous solution was extracted three times with ether. The organic phase was washed with water until the washings were neutral, dried over magnesium sulfate and concentrated on a rotary evaporator.

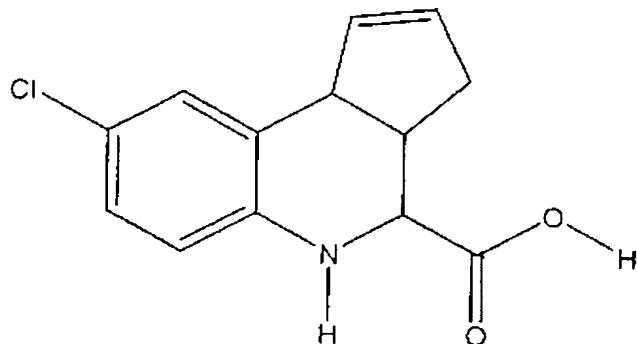
5 An ESI-MS was run to characterize the product:

MS (EI) m/z: 284 (M*)

Example 2

10

8-Chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid (**2**)



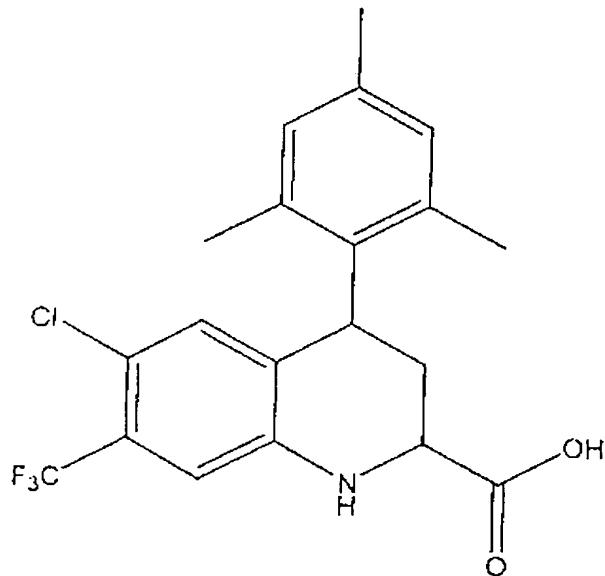
15

Compound **2** was saponified with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol. The ethanolic solution was concentrated on a rotary evaporator, the residue was taken up in water, 6 N HCl was added and the aqueous solution was extracted three times with ether. The organic phase was washed with water until the washings were neutral, dried over magnesium sulfate and concentrated on a rotary evaporator.

An ESI-MS was run to characterize the product:

25

MS (EI) m/z: 250 (M*)

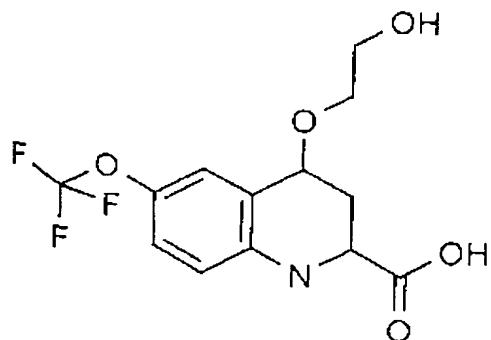
Example 3

5 6-Chloro-7-trifluoromethyl-4-(2,4,6-trimethylphenyl)-
1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**3**)

Compound **3** was prepared by the basic process from 5.0 mmol
of 4-chloro-4-trifluoromethylaniline, 5.5 mmol of glyoxalic
10 acid monohydrate and 15.0 mmol of 2,4,6-trimethylstyrene in
30 ml of acetonitrile.

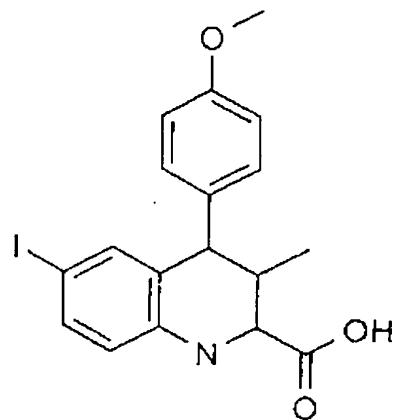
An ESI-MS was run to characterize the product:

15 MS (EI) m/z: 398.1 (M*)

Example 4

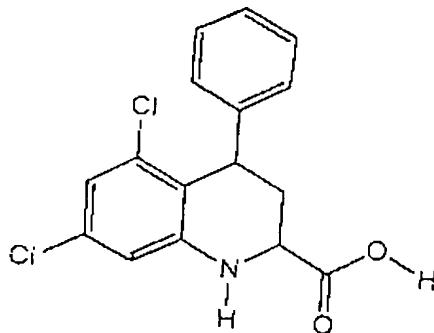
5 4-(2-Hydroxyethoxy)-6-trifluoromethoxy-1,2,3,4-
tetrahydroquinoline-2-carboxylic acid (**4**)

Compound **4** was prepared by the automated process from 4-
(trifluoromethoxy)aniline, glyoxylic acid and ethylene
10 glycol monovinyl ether.

Example 5

15 6-Iodo-4-(4-methoxyphenyl)-3-methyl-1,2,3,4-
tetrahydroquinoline-2-carboxylic acid (**5**)

Compound **5** was prepared by the automated process from 4-
20 iodoaniline, glyoxylic acid and trans-anethole.

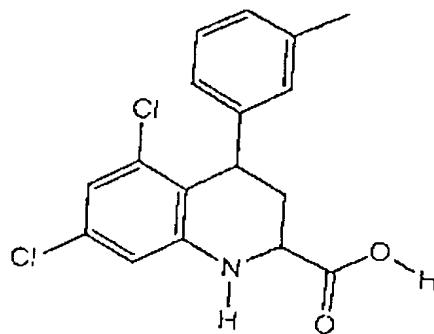
Example 6

5 5,7-Dichloro-4-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**6**)

Compound **6** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of styrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

15 An ESI-MS was run to characterize the product:

MS (EI) m/z: (M*) 315

Example 7

20

5,7-Dichloro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-

carboxylic acid (7)

Compound **7** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate

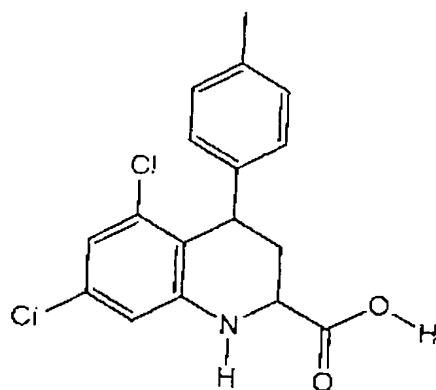
5 solution (50%, toluene), 15.0 mmol of 3-methylstyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

10 An ESI-MS was run to characterize the product:

MS (EI) m/z: (M*) 335

Example 8

15



5,7-Dichloro-4-p-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**8**)

20

Compound **8** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 4-methylstyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of

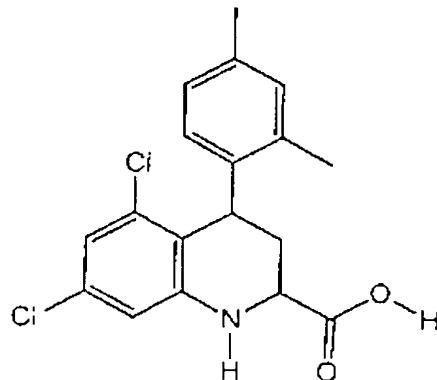
25 acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

An ESI-MS was run to characterize the product:

MS (EI) m/z: (M*) 335

Example 9

5



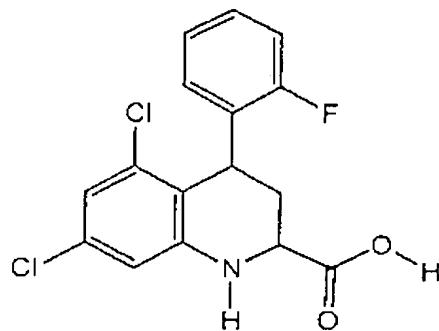
5,7-Dichloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**9**)

10

Compound **9** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 2,4-dimethylstyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

An ESI-MS was run to characterize the product:

20 MS (EI) m/z: (M*) 349

Example 10

5 5,7-Dichloro-4-(2-fluorophenyl)-1,2,3,4-
tetrahydroquinoline-2-carboxylic acid (**10**)

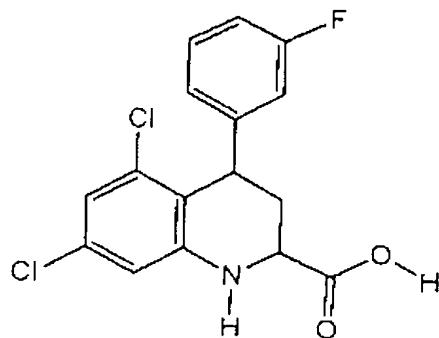
10 Compound **10** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 2-fluorostyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

15 An ESI-MS was run to characterize the product:

MS (EI) m/z: (M*) 339

Example 11

20



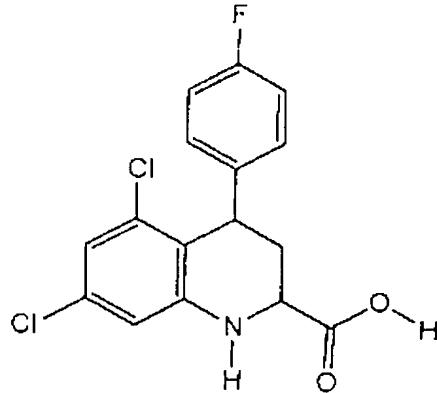
5,7-Dichloro-4-(3-fluorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**11**)

Compound **11** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 3-fluorostyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

An ESI-MS was run to characterize the product:

MS (EI) m/z: (M*) 340

15 **Example 12**



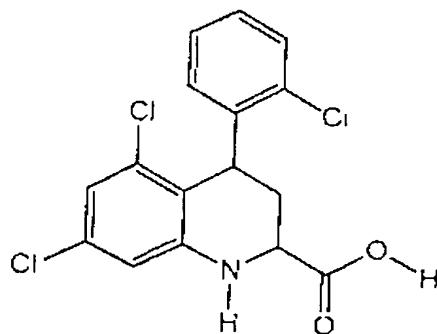
20 5,7-Dichloro-4-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**12**)

Compound **12** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 4-fluorostyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

An ESI-MS was run to characterize the product:

MS (EI) m/z: (M*) 340

5 **Example 13**



5,7-Dichloro-4-(2-chlorophenyl)-1,2,3,4-

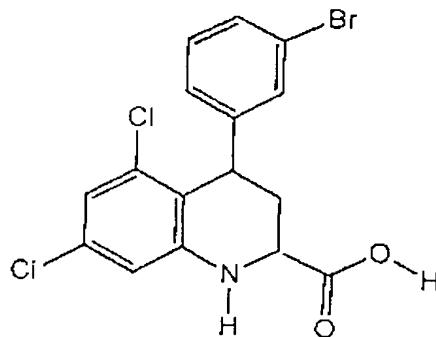
10 tetrahydroquinoline-2-carboxylic acid (**13**)

Compound **13** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 2-chlorostyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

An ESI-MS was run to characterize the product:

20

MS (EI) m/z: (M*) 356

Example 14

5 4-(3-Bromophenyl)-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**14**)

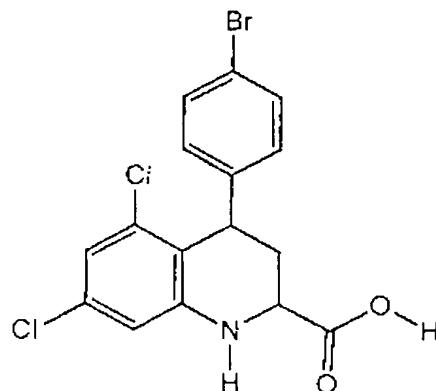
10 Compound **14** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 3-bromostyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

15 An ESI-MS was run to characterize the product:

MS (EI) m/z: (M*) 401

Example 15

20



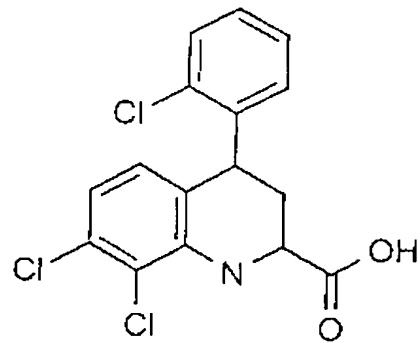
4-(4-Bromophenyl)-5,7-dichloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**15**)

Compound **15** was prepared by the basic process from 5.0 mmol of 3,5-dichloroaniline, 5.5 mmol of ethyl glyoxalate solution (50%, toluene), 15.0 mmol of 4-bromostyrene and 5.0 mmol of trifluoroacetic acid in 30.0 ml of acetonitrile. The subsequent saponification was carried out with 1.0 ml of sodium hydroxide solution (6 N, water) in 20.0 ml of ethanol.

An ESI-MS was run to characterize the product:

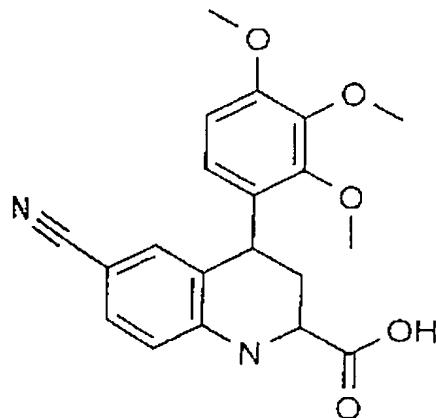
MS (EI) m/z: (M⁺) 401

15 Example 16



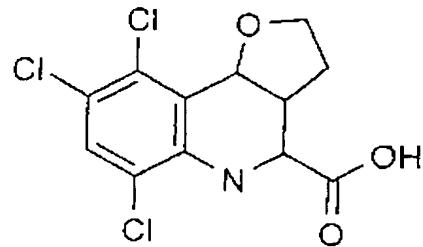
7,8-Dichloro-4-(2-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**16**)

Compound **16** was prepared by the automated process from 2,3-dichloroaniline, glyoxylic acid and 2-chlorostyrene.

Example 17

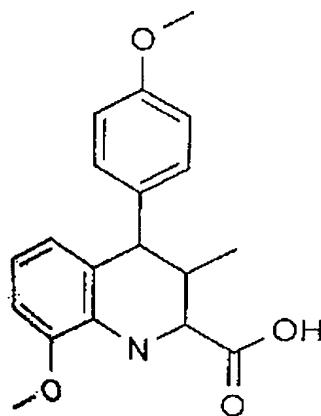
5 6-Cyano-4-(2,3,4-trimethoxyphenyl)-1,2,3,4-
tetrahydroquinoline-2-carboxylic acid (**17**)

Compound **17** was prepared by the automated process from 4-aminobenzonitrile, glyoxylic acid and 2,3,4-tetramethoxystyrene.

Example 18

15 6,8,9-Trichloro-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]-
quinoline-4-carboxylic acid (**18**)

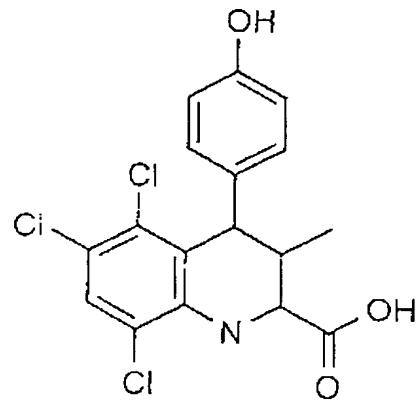
Compound **67** was prepared by the automated process from 20 2,4,5-trichloroaniline, glyoxylic acid and 2,3-dihydrofuran.

Example 19

5 8-Methoxy-4-(4-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**19**)

Compound **19** was prepared by the automated process from 2-methoxyaniline, glyoxylic acid and *trans*-anethole.

10

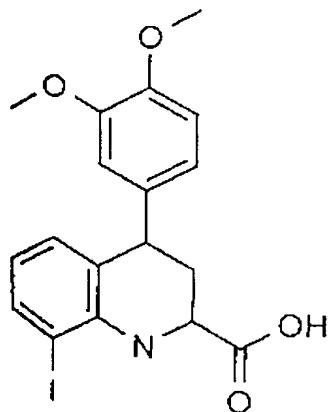
Example 20

15 5,6,8-Trichloro-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**20**)

Compound **20** was prepared by the automated process from 2,3,5-trichloroaniline, glyoxylic acid and 2-

propenylphenol.

Example 21

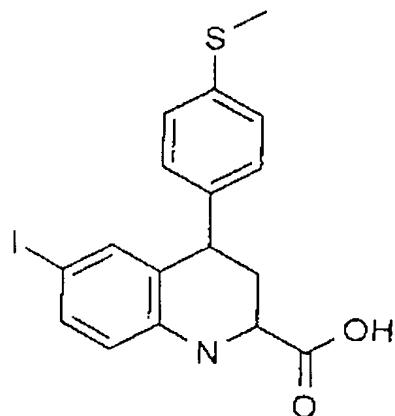


5

4-(3,4-Dimethoxyphenyl)-8-iodo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**21**)

10 Compound **21** was prepared by the automated process from 2-iodoaniline, glyoxylic acid and 3,4-dimethoxystyrene.

Example 22

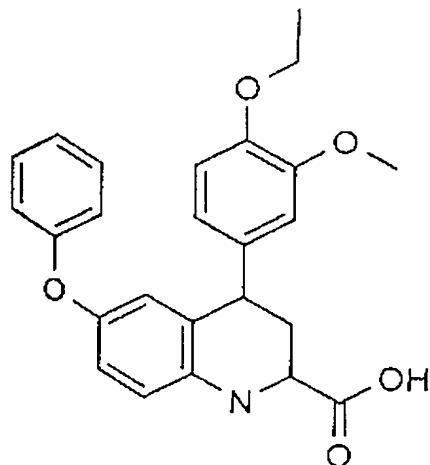


15

6-Iodo-4-(4-methylsulfonylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**22**)

Compound **22** was prepared by the automated process from 4-iodoaniline, glyoxylic acid and 1-methylsulfanyl-4-vinylbenzene.

5 **Example 23**

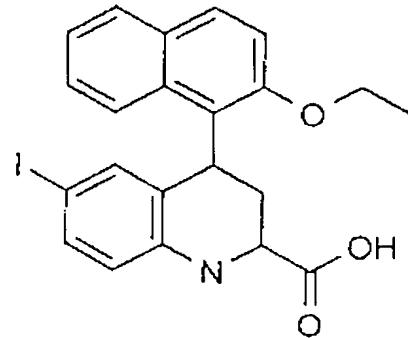


10 4-(4-Ethoxy-3-methoxyphenyl)-6-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**23**)

Compound **23** was prepared by the automated process from 4-phenoxyaniline, glyoxylic acid and 1-ethoxy-2-methoxy-4-vinylbenzene.

15

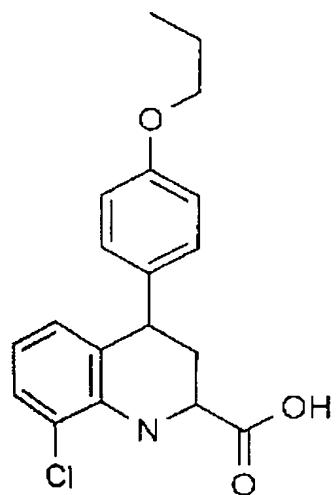
Example 24



4-(2-Ethoxynaphthalen-1-yl)-6-iodo-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**24**)

Compound **24** was prepared by the automated process from 4-
5 iodoaniline, glyoxylic acid and 2-ethoxy-1-vinylnaphthalene.

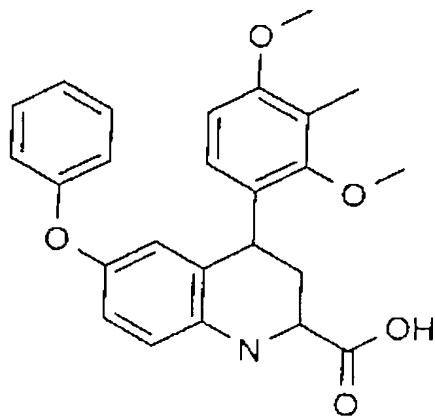
Example 25



10

8-Chloro-4-(4-propoxypyphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (**25**)

15 Compound **25** was prepared by the automated process from 2-chloroaniline, glyoxylic acid and 4-propoxystyrene.

Example 26

5 4-(2,4-Dimethoxy-3-methylphenyl)-6-phenoxy-1,2,3,4-
tetrahydroquinoline-2-carboxylic acid (**26**)

Compound **26** was prepared by the automated process from 4-phenoxyaniline, glyoxylic acid and 2,4-dimethoxy-3-methylstyrene.

10 Examples 27 to 102 were prepared analogously.

Example	Name
27	4-anthracen-9-yl-6-chloro-8-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
28	6-sec-butyl-4-naphthalen-1-yl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
29	4-(4-hydroxyphenyl)-3-methyl-8-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
30	8-chloro-6-fluoro-4-naphthalen-2-yl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
31	4-(4-methoxyphenyl)-3-methyl-6-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
32	6-chloro-8-fluoro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
33	8-chloro-6-fluoro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
34	4-(4-bromophenyl)-6-chloro-8-fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
35	7,8-dichloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
36	6-chloro-4-(4-chlorophenyl)-7-trifluoromethyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
37	4-(2-chlorophenyl)-6-cyano-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
38	6-bromo-8-chloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
39	6-bromo-4-(2-bromophenyl)-8-chloro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
40	4-(4-hydroxy-3-methoxyphenyl)-3-methyl-6-methylsulfanyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
41	6-cyano-3,4-bis(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
42	ethyl 8-chloro-6-fluoro-3,4-bis(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylate
43	5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
44	5,7-dichloro-4-(3-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
45	5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
46	1,3-dichloro-5,6,6a,7,8,12b-hexahydrobenzo[k]-phenanthridine-6-carboxylic acid
47	1,3-dichloro-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]quinoline-6-carboxylic acid
48	5,7-dichloro-4-(3,5-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid
49	7,9-dichloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]quinoline-4-carboxylic acid

Example 50

Receptor binding (glycine binding site of the NMDA receptor channel)

5

The tests for determining the affinity of the compounds of formula I according to the invention for the glycine binding site of the NMDA receptor channel were carried out on brain membrane homogenates (homogenate of the cortex and hippocampus areas of the brain of male rats, Wistar strain) [B.M. Baron, B.W. Siegel, B.L. Harrison, R.S. Gross, C. Hawes and P. Towers, *Journal of Pharmacology and Experimental Therapeutics*, vol. 279, p. 62, 1996].

15 For this purpose, the cortex and hippocampus were freed without cutting from freshly removed rat brains, homogenized in 5 mmol/l TRIS acetate buffer, 0.32 mol/l sucrose, pH 7.4 (10 ml/g of fresh weight), using a Potter homogenizer (Braun/Melsungen, 10 piston strokes at 500 rpm), with ice cooling, and then centrifuged for 10 minutes at 1000 g and 4°C. The first supernatant was collected and the sediment was homogenized again with 5 mmol/l TRIS acetate buffer, 0.32 mol/l sucrose, pH 7.4 (5 ml/g of original fresh weight), using the Potter homogenizer (10 piston strokes at 500 rpm), with ice cooling, and centrifuged for 10 minutes at 1000 g and 4°C. The resulting supernatant was combined with the supernatant from the first centrifugation and centrifuged at 17,000 g for 20 minutes at 4°C. The supernatant after this centrifugation was discarded and the membrane sediment was taken up with 5 mmol/l TRIS acetate buffer, pH 8.0 (20 ml/g of original fresh weight), and homogenized with 10 piston strokes at 500 rpm.

35 The membrane homogenate was then incubated for 1 hour at 4°C and centrifuged for 30 minutes at 50,000 g and 4°C. The

supernatant was discarded and the centrifuge tube containing the membrane sediment was sealed with Parafilm and frozen for 24 hours at -20°C. On the following day the membrane sediment was thawed, taken up with ice-cold 5 mmol/l TRIS acetate buffer, 0.1% saponin (w/v), pH 7.0 (10 ml/g of original fresh weight), homogenized with 10 piston strokes at 500 rpm and then centrifuged for 20 minutes at 50,000 g and 4°C. The resulting supernatant was discarded and the sediment was taken up in a small volume 10 with 5 mmol/l TRIS acetate buffer, pH 7.0 (approx. 2 ml/g of original fresh weight), and homogenized again with 10 piston strokes at 500 rpm. After determination of the protein content, the membrane homogenate was adjusted to a protein concentration of 10 mg protein/ml with 5 mmol/l 15 TRIS acetate buffer, pH 7.0, and frozen in aliquots until tested.

For the receptor binding test, aliquots were thawed, diluted to 1:10 with 5 mmol/l TRIS acetate buffer, pH 7.0, 20 homogenized with 10 piston strokes at 500 rpm using the Potter homogenizer (10 piston strokes at 500 rpm), with ice cooling, and centrifuged for 60 minutes at 55,000 g and 4°C. The supernatant was decanted and the membrane sediment was adjusted to a protein concentration of 1 mg/ml with ice- 25 cold 50 mmol/l TRIS acetate buffer, pH 7.0, homogenized again with 10 piston strokes at 500 rpm and kept in suspension by stirring on a magnetic stirrer in an ice bath. 100 µl aliquots of this membrane homogenate were used per ml of preparation in the receptor binding test 30 (0.1 mg protein/ml in the final preparation).

In the binding test, 50 mmol/l TRIS acetate buffer, pH 7.0, was used as the buffer and 1 nmol/l (³H)-MDL 105.519 (B.M. Baron et al., 1996) was used as the radioactive ligand. 35 The proportion of non-specific binding was determined in the presence of 1 mmol/l glycine.

In other preparations the compounds according to the invention were added in concentration series and the displacement of the radioactive ligand from its specific binding to the glycine binding site of the NMDA receptor channel was measured. The preparations, in triplicate in each case, were incubated for 120 minutes at 4°C and then harvested by means of filtration through glass fibre filter mats (GF/B) in order to determine the radioactive ligand bound to the membrane homogenate. The radioactivity retained on the glass fibre filters was measured in a β counter after the addition of scintillator.

The affinity of the compounds according to the invention for the glycine binding site of the NMDA receptor channel was calculated as the IC_{50} value (concentration causing 50% displacement of the radioactive ligand from its specific binding) according to the law of mass action by means of non-linear regression and is indicated in Table 1 as the Ki value (mean of 3 independent experiments) after conversion (according to the Cheng-Prussoff relationship), or as the percentage of the previously bound radioactive ligand (see above) which is displaced from its specific binding by a concentration of 10 $\mu\text{mol/l}$ of the substance according to the invention to be tested.

25

Table 1:

Example	Glycine binding site of the NMDA receptor channel	
	Ki ($\mu\text{mol/l}$)	Displacement (% , 10 $\mu\text{mol/l}$)
2	0.3	100

Example 51

NMDA/glycine-induced ionic fluxes on RNA-injected *Xenopus* oocytes

5

The test to determine functional changes of the NMDA receptor channel due to the compound of formula I according to the invention was performed on oocytes of the South African clawed frog, *Xenopus laevis*. This was done by 10 forming neuronal NMDA receptor channels in oocytes after the injection of rat brain RNA and measuring ionic fluxes triggered by the coapplication of NMDA and glycine.

Stage V and VI *Xenopus* oocytes (Dumont, J.N., Journal of Morphology, vol. 136, 1972) were microinjected with total RNA from adult rat brain tissue (100-130 ng/cell) and kept at 20°C for up to 10 days in culture medium (composition in mmol/l: 88.0 NaCl, 1.0 KCl, 1.5 CaCl₂, 0.8 MgSO₄, 2.4 NaHCO₃, 5 HEPES, 100 IU/ml penicillin, 100 µg/ml

streptomycin, pH 7.4). Transmembrane ionic fluxes were recorded by the conventional two-electrode voltage clamp technique at a holding potential of -70 mV (P. Bloms-Funke, P.M. Madeja, U. Musshoff, E.-J. Speckmann, Neuroscience Letters, vol. 205, p. 115, 1996). The data were plotted 25 and the experimental apparatus controlled using the OTC interface and Cellworks software (npi, FRG). The compounds according to the invention were added to a nominally Mg²⁺-free medium (composition in mmol/l: 89.0 NaCl, 1.0 KCl, 1.8 CaCl₂, 2.4 NaHCO₃, 5 HEPES, pH 7.4) and applied 30 systemically by means of a concentration clamp (npi, FRG).

To test substance effects mediated via the glycine B binding site of the NMDA receptor channel, the glycine dose-effect curve was plotted with and without the particular compound according to the invention. To do 35 this, NMDA in a fixed concentration of 100 µmol/l was cumulatively coapplied with glycine in increasing

concentrations (0-100 $\mu\text{mol/l}$). The experiment was then repeated in the same manner with a fixed concentration of the compound according to the invention. To estimate the selectivity for NMDA versus AMPA receptor channels, the 5 effects of the compound according to the invention (10 $\mu\text{mol/l}$) was additionally studied on ionic fluxes triggered by AMPA (100 $\mu\text{mol/l}$). The current amplitudes were normalized to that of the control response to the coapplication of NMDA (100 $\mu\text{mol/l}$) with glycine 10 (10 $\mu\text{mol/l}$). The data were analyzed with Igor-Pro software (Version 3.1, WaveMetrics, USA). All the results were expressed as the mean \pm standard error (SEM) of at least 3 experiments on different oocytes from at least two frogs. The significance for unpaired and paired measurable 15 variables is determined by the Mann-Whitney U-test and the Wilcoxon test (Sysstat, SPSS Inc., USA) respectively. EC₅₀ values are calculated according to the following formula:

$$Y = Y_{\min} + (Y_{\max} - Y_{\min}) / (1 + (X/EC_{50})^{-p})$$

20 (Y_{min} = minimum test value, Y_{max} = maximum test value, Y = relative current amplitude, X = concentration of test substance, p = slope factor). On right shifting of the glycine dose-effect curve, the pA₂ value of the compound 25 according to the invention was determined graphically by means of Schild regression. Concentration ratios were calculated using the EC₅₀ values, which were determined independently for each dose-effect curve.

30 The right shifting of the glycine dose-effect curve is shown for Example no. 1 (relative amplitude: current amplitude, normalized to the response after application of NMDA/glycine (100/10 $\mu\text{mol/l}$)). The results for selected compounds according to the invention in respect of their 35 effects on the glycine dose-effect curve and on AMPA-induced ionic fluxes have been collated in Table 2.

Table 2: Effects of the compounds according to the invention on ionic fluxes triggered by NMDA/glycine and AMPA on RNA-injected oocytes

Example no.	NMDA/glycine-induced ionic fluxes pA₂ value relating to the glycine dose-effect curve	AMPA-induced ionic fluxes Inhibition at 10 µmol/l of the compounds according to the invention
1	6.40	5.4% (n = 2)

5

Example 52

Formalin test on the rat

10 The experiments for determining the antinociceptive action of the compounds of formula I according to the invention were performed in the formalin test on male rats (Sprague-Dawley, 150 - 170 g).

15 In the formalin test a distinction is made between the first (early) phase (0 - 15 min after the formalin injection) and the second (late) phase (15 - 60 min after the formalin injection) (D. Dubuisson, S.G. Dennis, Pain, 4, 161 - 174 (1977)). The early phase represents a model

20 for acute pain as a direct reaction to the formalin injection, while the late phase is regarded as a model for persistent (chronic) pain (T.J.Coderre, J. Katz, A.L. Vaccarino, R. Melzack, Pain, vol. 52, p. 259, 1993).

25 The compounds according to the invention were studied in the second phase of the formalin test in order to make predictions about the actions of substances on chronic/inflammatory pain.

30 A single subcutaneous formalin injection (50 µl, 5%) in the dorsal side of the right back paw of free-moving

experimental animals induced a nociceptive reaction which is represented by the following behavioural parameters: lifting and holding of the affected paw (score 1), shaking or twitching (score 2), licking and biting (score 3). The 5 differing modes of behaviour triggered by the formalin injection were recorded continuously by observing the animals in the late phase of the formalin test, and differently weighted in an evaluation. Normal behaviour, where the animal distributes its weight evenly over all 10 four paws, was recorded as a score of 0. The time of administration before the formalin injection was chosen according to the mode of administration of the compounds according to the invention (intraperitoneal: 15 min, intravenous: 5 min). After the injection of substances 15 that have an antinociceptive action in the formalin test, the described modes of behaviour (score 1 - 3) of the animals are reduced or even eliminated. The comparison was made with control animals which had received vehicle (solvent) before the administration of formalin. The 20 nociceptive behaviour was calculated as the so-called pain rate (PR). The different behavioural parameters were differently weighted (factor 0, 1, 2, 3). The calculation was performed in subintervals of 3 min according to the following formula:

25

$$PR = [(T_0 \times 0) + (T_1 \times 1) + (T_2 \times 2) + (T_3 \times 3)]/180$$

30 T_0 , T_1 , T_2 and T_3 corresponding to the time in seconds in which the animal exhibited the mode of behaviour 0, 1, 2 or 3, respectively. The number of animals in the substance and vehicle groups, n , is 10 in each case. Based on the PR calculations, the substance effect was determined as a percentage change relative to the control. The ED_{50} calculations were performed by regression analysis.

35

All the compounds according to the invention which were

tested showed a moderately strong to strong inhibition of the formalin-induced nociception.

5 The results of selected studies in the formalin test on the rat are collated in the Table below.

Table 3:

Compound	Mode of administration	Dose [mg/kg]	% inhibition of the formalin-induced nociception
1	i.p.	21.5	64.5

10 **Example 53: General preparation of the salts according to the invention from the compounds of one of Examples 1-49**

15 One equivalent of the compound of one of Examples 1 to 49, preferably an imino acid or carboxylic acid, is suspended in a small volume of water and one equivalent of 1 N aqueous alkaline solution, preferably NaOH or KOH, is added. If the solubility is poor, methanol is added dropwise until the compound has completely dissolved.

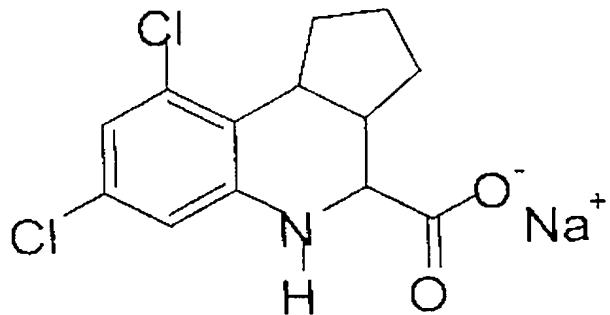
20 After stirring for 30 minutes at room temperature, the solution is concentrated on a rotary evaporator and the residual solution is frozen at -60°C in an isopropanol/dry ice mixture and freeze-dried. The salts, especially of imino acids and preferably the sodium or potassium salts, 25 are usually obtained as colourless solids.

30 An alternative possibility is to prepare the potassium or sodium salts with potassium or sodium trimethylsilanolate (E.D. Laganis, B.L. Chenard, Tetrahedron Letters, 25, 5831-5834 (1984)). Potassium or sodium trimethylsilanolate is dissolved under nitrogen in an organic solvent (dichloromethane, toluene, THF) and the ester or acid is added all at once. The reaction mixture is stirred for

four hours at room temperature and filtered. The usually colourless solid is washed with diethyl ether and dried under vacuum. The potassium or sodium salts are obtained as solids.

5

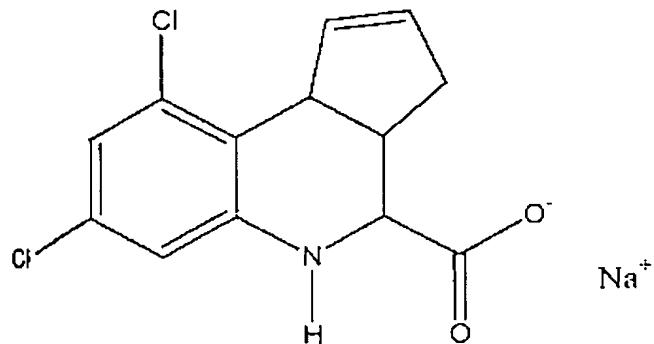
Example 54



10 7,9-Dichloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]-
quinoline-4-carboxylate; sodium salt (**54**)

15 7,9-Dichloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]-
quinoline-4-carboxylic acid (**49**) is treated according to
Example 106 to give 7,9-dichloro-2,3,3a,4,5,9b-hexahydro-
1H-cyclopenta[c]quinoline-4-carboxylate; sodium salt (**54**).

Example 55



20

7,9-Dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-4-carboxylate; sodium salt (**55**)

Compound 1 prepared according to Example 1 is treated
5 according to Example 53 to give 7,9-dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylate; sodium salt (**55**).

Molecular weight calculated by ESI-MS: 284.14 g/mol;
10 measured molecular weight: 282.3 (M-H), 238.4 (M-CO₂).

¹H NMR (d₆-DMSO/TMS_{ext}): δ = 2.15 – 2.40 ppm (m, 2H, CH₂);
3.35 ppm (q, 1H, CH); 3.50 ppm (m, 1H, CH); 4.05 ppm (dd,
1H, CH); 5.60 ppm (m, 1H, olefin H); 5.70 ppm (m, 1H, NH);
15 5.80 ppm (M, 1H, olefin CH); 6.60 ppm (d, 1H, aryl CH);
6.85 ppm (d, 1H, aryl CH).

Example 56: Receptor binding of the salts according to the invention at the glycine binding site of the NMDA receptor channel

Compounds **54** and **55** are studied for receptor binding as explained in Example 50:

25 Table 4:

Example	Glycine binding site of the NMDA receptor channel	
	K _i (μmol/l)	Displacement (% , 10 μmol/l)
54		97
55	0.35	90

Example 57: Formalin test

30 Compound **55** was studied in the formalin test as described in Example 52.

Table 5:

Compound	Mode of administration	Dose [mg/kg]	% inhibition of the formalin-induced nociception
55	i.v.	68.1	56

Example 58: Parenteral mode of administration

5

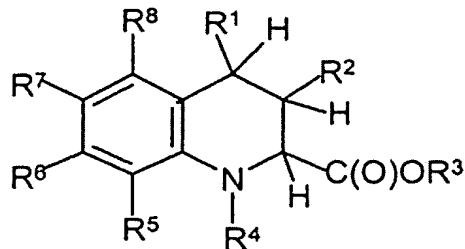
38.5 g of compound **55** are dissolved in 1 l of water for injection at room temperature and then adjusted to isotonic conditions by the addition of anhydrous glucose for injection.

10

Claims

1. Substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives of general formula I:

5



I,

in the form of their physiologically acceptable salts with cations or bases, optionally in the form of their racemates or their pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially the enantiomers or diastereoisomers, in any desired mixing ratio,

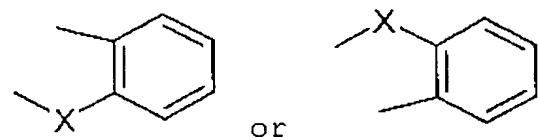
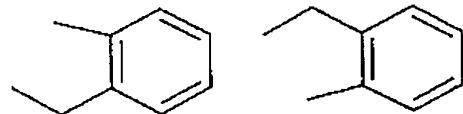
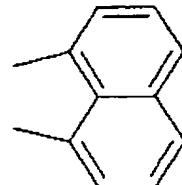
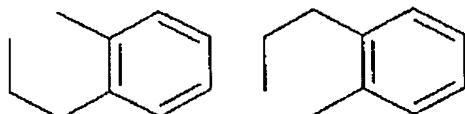
15 in which

either

R¹ and **R²** together form the following, each of which is 20 monosubstituted or polysubstituted or unsubstituted:

- (CH₂)_n-, where n = 3-10,
 -CH=CH-CH₂-, -CH₂-CH=CH-,
 -CH=CH-CH₂-CH₂-, -CH₂-CH₂-CH=CH-,
 25 -CH₂-CH=CH-CH₂-,
 -CH₂-CH=CH-CH₂-CH₂-, -CH₂-CH₂-CH=CH-CH₂-,
 -CH₂-CH₂-CH=CH-CH₂-CH₂-,
 -O-CH₂-CH₂-, -CH₂-CH₂-O-,
 -O-CH₂-CH₂-CH₂-, -CH₂-CH₂-CH₂-O-,

$$\begin{aligned} & -\text{CH}_2-\text{O}-\text{CH}_2-, \\ & -\text{CH}_2-\text{CH}_2-\text{O}-\text{CH}_2-, \quad -\text{CH}_2-\text{O}-\text{CH}_2-\text{CH}_2-, \end{aligned}$$



$x = 0, s$

5

\mathbf{R}^3 is selected from

10 H; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by N, S or O; alkylaryl or
15 alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or

heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

R⁴ is selected from

5

R^{4a} or ZR^{4a}, where Z = C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and R^{4a} is selected from

10

H; C₁-C₁₂-alkyl, C₂-C₁₂-alkenyl or C₂-C₁₂-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

15

20

C(O)R⁹, C(O)OR⁹, C(S)R⁹, C(S)OR⁹ or S(O₂)R⁹, where R⁹ is selected from

25

H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding

30

heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each

35

of which is monosubstituted or polysubstituted or unsubstituted, especially phenethyl, 1-adamantyl, 2-adamantyl, 1-naphthyl or 2-naphthyl, 2-, 3- or 4-pyridyl or thiazolyl;

5

SR¹⁰, where R¹⁰ is selected from

10

aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

15

C(O)NR¹¹R¹², C(O)NR¹¹NR¹²R¹³, C(NR¹¹)NR¹²R¹³, C(S)NR¹¹R¹² or C(S)NR¹¹NR¹²R¹³, where R¹¹, R¹² and R¹³ independently of one another are selected from

20

H; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

25

30

R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

35

H; F; Cl; Br; I; CN; NO₂; and C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or

unbranched and monosubstituted or polysubstituted or unsubstituted;

10 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

15

20

$\text{NR}^{15}\text{R}^{16}$, $\text{NR}^{15}\text{C}(\text{O})\text{R}^{16}$, $\text{C}(\text{NR}^{15})\text{NR}^{16}\text{R}^{17}$, $\text{NR}^{15}\text{C}(\text{S})\text{R}^{16}$, $\text{C}(\text{S})\text{NR}^{15}\text{R}^{16}$, $\text{C}(\text{S})\text{NR}^{15}\text{NR}^{16}\text{R}^{17}$ or $\text{S}(\text{O}_2)\text{NR}^{15}\text{R}^{16}$, where R^{15} , R^{16} and R^{17} independently of one another are selected from

25 H; O; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of

which is monosubstituted or polysubstituted or unsubstituted;

or

5

R¹⁵ and R¹⁶ or R¹⁶ and R¹⁷ together form a C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; or

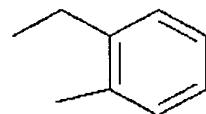
R⁵ and **R**⁶, **R**⁶ and **R**⁷ or **R**⁷ and **R**⁸ together form

15 $=CR^{18}-CH=CH-CH-$ or $=CH-CR^{18}=CH-CH=$, where R^{18} is selected from

20 H; F; Cl; Br; I; OH; and C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted,

with the proviso that

25 if R^1 and R^2 together form $-CH=CH-CH_2-$ or



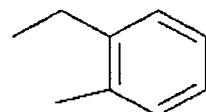
30 and R³ is (-)-p-menthan-3-ol, especially menthol or borneol, R⁷ ≠ Cl and R⁵, R⁶ and R⁸ ≠ H simultaneously,

if R^1 and R^2 together form $-CH=CH-CH_2-$ and R^3 is CH_3 , $R^7 \neq H$, Cl or OCH_3 and R^5 , R^6 and $R^8 \neq H$ simultaneously,

if R^{1b} and R^{2a} together form $-CH=CH-CH_2-$ and R^3 is H, $R^7 \neq OCH_3$ or $C(O)NH_2$ and R^5 , R^6 and $R^8 \neq H$, R^5 and $R^7 \neq CH_3$ and R^6 and $R^8 \neq H$, or $R^5 \neq OCH_3$ and R^6 , R^7 and $R^8 \neq H$ simultaneously, or

5

if R^{1b} and R^{2a} together form



10 or $-O-CH_2-CH_2-$ and R^3 is C_2H_5 , $R^7 \neq H$, Cl, CH_3 , OCH_3 or NO_2 and R^5 , R^6 and $R^8 \neq H$, or $R^5 \neq NO_2$ and R^6 , R^7 and $R^8 \neq H$ simultaneously;

or

15

R^1 is selected from

20 C_1-C_{10} -alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C_3-C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl which is monosubstituted or polysubstituted or 25 unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

OR¹⁹, SR¹⁹ or SO₂R¹⁹, where R¹⁹ is selected from

30 C_1-C_{10} -alkyl, C_2-C_{10} -alkenyl or C_2-C_{10} -alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C_3-C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or

polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; and alkylaryl, aryl, alkylheteroaryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

R² is selected from

H; C₁-C₁₀-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and phenyl which is monosubstituted or polysubstituted or unsubstituted, where if **R²** is phenyl, **R¹** must be aryl, O-aryl or S-aryl;

15

R³ is selected from

H; C₁-C₁₈-alkyl, C₂-C₁₈-alkenyl or C₂-C₁₈-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by N, S or O; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

25

30 **R⁴** is selected from

R^{4a} or ZR^{4a}, where Z = C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and R^{4a} is selected from

35

H; C₁-C₁₂-alkyl, C₂-C₁₂-alkenyl or C₂-C₁₂-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

5 C(O)R⁹, C(O)OR⁹, C(S)R⁹, C(S)OR⁹ or S(O₂)R⁹, where R⁹ is selected from

15 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted, especially phenethyl, 1-adamantyl, 2-adamantyl, 1-naphthyl or 2-naphthyl, 2-, 3- or 4-pyridyl or thiazolyl;

20 25 30

35 SR¹⁰, where R¹⁰ is selected from

aryl or heteroaryl, each of which is monosubstituted or polysubstituted or

unsubstituted;

5 $C(O)NR^{11}R^{12}$, $C(O)NR^{11}NR^{12}R^{13}$, $C(NR^{11})NR^{12}R^{13}$,
 $C(S)NR^{11}R^{12}$ or $C(S)NR^{11}NR^{12}R^{13}$, where R^{11} , R^{12} and R^{13}
 independently of one another are selected from

10 H ; C_1 - C_{18} -alkyl, C_2 - C_{18} -alkenyl or C_2 - C_{18} -
 alkynyl, each of which is branched or
 unbranched and monosubstituted or
 polysubstituted or unsubstituted; C_3 - C_8 -
 cycloalkyl which is saturated or unsaturated
 and monosubstituted or polysubstituted or
 unsubstituted, or a corresponding
 heterocycle in which at least one ring C
15 atom is replaced by S, O or N; alkylaryl or
 alkylheteroaryl, each of which is
 monosubstituted or polysubstituted or
 unsubstituted; and aryl or heteroaryl, each
 of which is monosubstituted or
20 polysubstituted or unsubstituted;

R^5 , R^6 , R^7 and R^8 independently of one another are selected
from

25 H ; F; Cl; Br; I; CN; NO_2 ; and C_1 - C_{10} -alkyl, C_2 - C_{10} -
 alkenyl or C_2 - C_{10} -alkynyl, each of which is branched or
 unbranched and monosubstituted or polysubstituted or
 unsubstituted;

30 OR^{14} , $OC(O)R^{14}$, $OC(S)R^{14}$, $C(O)R^{14}$, $C(O)OR^{14}$, $C(S)R^{14}$,
 $C(S)OR^{14}$, SR^{14} , $S(O)R^{14}$ or $S(O_2)R^{14}$, where R^{14} is selected
 from

35 H ; C_1 - C_{10} -alkyl, C_2 - C_{10} -alkenyl or C_2 - C_{10} -alkynyl,
 each of which is branched or unbranched and
 monosubstituted or polysubstituted or

unsubstituted; C_3 - C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

15 $NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $C(NR^{15})NR^{16}R^{17}$, $NR^{15}C(S)R^{16}$, $C(S)NR^{15}R^{16}$, $C(S)NR^{15}NR^{16}R^{17}$ or $S(O_2)NR^{15}R^{16}$, where R^{15} , R^{16} and R^{17} independently of one another are selected from

20 H; O; C_1 - C_{18} -alkyl, C_2 - C_{18} -alkenyl or C_2 - C_{18} -alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C_3 - C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted;

25 30 or

35 R^{15} and R^{16} or R^{16} and R^{17} together form a C_3 - C_8 -cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one C atom is replaced by S, O or

N; or

R⁵ and **R**⁶, **R**⁶ and **R**⁷ or **R**⁷ and **R**⁸ together form

10 H; F; Cl; Br; I; OH; and C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted,

with the proviso that

15 if R^4, R^6, R^7 and $R^8 = H$,

- $R^1 \neq CH_3$, $R^3 \neq H$ or CH_3 and R^2 and $R^5 \neq H$ simultaneously;
or
- $R^1 \neq$ unsubstituted phenyl, $R^3 \neq C_2H_5$ and R^2 and $R^5 \neq H$ simultaneously;

20

if R^4, R^5, R^6 and $R^8 = H$,

- $R^1 \neq S\text{-phenyl}$, $R^2 \neq H$, $R^7 \neq \text{Cl}$ and $R^3 \neq \text{CH}_3$ simultaneously;
or
- $R^1 \neq S\text{-2-pyridinyl}$, $R^2 \neq \text{CH}_3$, $R^7 \neq \text{OCH}_3$ and $R^3 \neq -\text{CH}_3\text{-CH=CH}_2$ simultaneously; or

if R^2 , R^4 , R^5 and R^7 = H and R^6 and R^8 = Cl,

- $R^1 \neq$ dioxalane and $R^3 \neq -CH_2-CH_2-OH$ simultaneously.

30 2. Salts according to Claim 1, characterized in that R⁴ is selected from

35 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and C₃-C₈-cycloalkyl which is saturated or unsaturated and

monosubstituted or polysubstituted or unsubstituted;
and

C(O)R⁹, where R⁹ is selected from

5 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl,
each of which is branched or unbranched and
monosubstituted or polysubstituted or
unsubstituted; C₃-C₈-cycloalkyl which is saturated
or unsaturated and monosubstituted or
10 polysubstituted or unsubstituted; and aryl or
heteroaryl, each of which is monosubstituted or
polysubstituted or unsubstituted, especially
phenethyl, 1-adamantyl, 2-adamantyl, 1-naphthyl
or 2-naphthyl, 2-, 3- or 4-pyridyl or thiazolyl.

15 3. Salts according to Claim 1 or 2, characterized in that
R⁴ is selected from

20 H; C₁-C₁₀-alkyl which is unsubstituted or
monosubstituted or polysubstituted; and phenyl which
is unsubstituted or monosubstituted or
polysubstituted, preferably H, CH₃ or C₂H₅ and
especially H.

25 4. Salts according to one of Claims 1 to 3, characterized
in that R³ is selected from

30 H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each
of which is branched or unbranched and monosubstituted
or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl
which is saturated or unsaturated and monosubstituted
or polysubstituted or unsubstituted, or a
corresponding heterocycle in which at least one ring C
atom is replaced by N or O; alkylaryl which is
35 monosubstituted or polysubstituted or unsubstituted;
and aryl or heteroaryl, each of which is

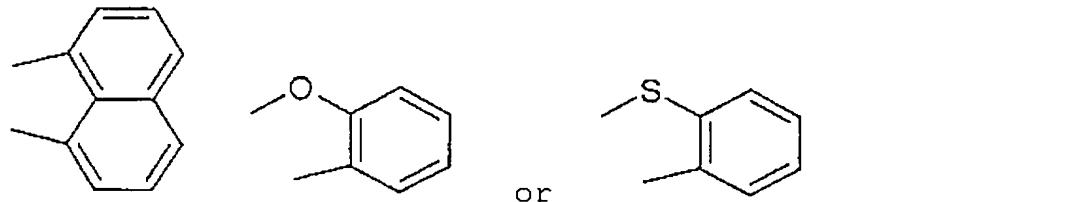
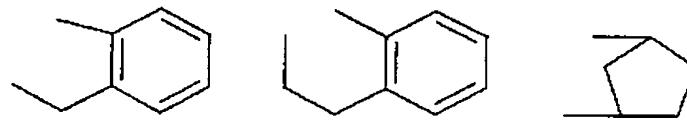
monosubstituted or polysubstituted or unsubstituted.

5. Salts according to one of Claims 1 to 4, characterized in that R³ is selected from

5 H; C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and phenyl, benzyl or phenethyl which is monosubstituted or polysubstituted or unsubstituted, 10 preferably H, CH₃ or C₂H₅ and especially H.

6. Salts according to one of Claims 1 to 5, characterized in that R¹ and R² together form

15 -O-CH₂-CH₂-, (-CH₂-)_n where n = 3-6, preferably 3 or 6, -CH=CH-CH₂-, -CH=CH-CH₂-CH₂-,



20 preferably -CH=CH-CH₂- or -CH=CH-CH₂-CH₂- and especially -CH=CH-CH₂-.

7. Salts according to one of Claims 1 to 5, characterized in that R¹ is selected from

25 phenyl, naphthyl or anthracenyl which is unsubstituted or monosubstituted or polysubstituted; and OR¹⁹ or SR¹⁹, where R¹⁹ is selected from

C₁-C₆-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

5

preferably anthracenyl, naphthyl or, in particular, phenyl which is unsubstituted or monosubstituted or polysubstituted by a substituent selected from

10

F; Cl; Br; I; methoxy; ethoxy; propoxy; methyl; ethyl; propyl (n-propyl, i-propyl); butyl (n-butyl, i-butyl, t-butyl); carboxyl; nitro; benzyloxy; phenyl; hydroxyl; phenoxy; trifluoromethyl; dioxolyl and SCH₃;

15

or OR¹⁹ or SR¹⁹, where R¹⁹ is selected from

20

C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; C₃-C₈-cycloalkyl which is saturated or unsaturated and monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

25

especially unsubstituted phenyl, naphthyl and anthracenyl, O-hydroxyethyl, ethoxynaphthyl, 4-hydroxy-3-methoxyphenyl, 4-propoxyphenyl, 2,3,4-trimethylphenyl, 2,4,5-trimethoxyphenyl, SCH₃, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2,6-dichlorophenyl, 4-carboxyphenyl, 3-nitrophenyl, 2,4,6-trimethylphenyl, 2,5-dimethylphenyl, 3,4-dimethoxyphenyl, 4-

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benzyloxy-3-methoxyphenyl, 3-methylphenyl, 4-methoxyphenyl,
4-biphenyl, 4-methylphenyl, 4-ethoxyphenyl, 2-methylphenyl,
2,4-dimethylphenyl, 2,6-dimethylphenyl, 4-hydroxy-3-
methoxyphenyl, 4-methylhydroxyphenyl, 4-hydroxyphenyl, 4-
5 phenoxyphenyl, 4-nitrophenyl, 4-chloromethylphenyl, 4-tert-
butylphenyl, 3,5-bis(trifluoromethyl)phenyl, 4-acetoxy-
phenyl, 4-cyanophenyl, 2-methoxyphenyl, 2,6-difluorophenyl,
2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-
trifluoromethylphenyl, 3-methoxyphenyl, 2-, 3- or 4-
10 benzyloxyphenyl, S-phenyl or 6-chlorobenzo[1,3]dioxol-5-yl.

8. Salts according to one of Claims 1 to 5 or 7,
characterized in that R² is selected from

15 H; C₁-C₄-alkyl which is branched or unbranched and
monosubstituted or polysubstituted or unsubstituted;
and phenyl which is monosubstituted or polysubstituted
or unsubstituted, preferably H, unsubstituted phenyl,
4-methoxyphenyl or CH₃ and especially H.

20 9. Salts according to one of Claims 1 to 8, characterized
in that R⁵, R⁶, R⁷ and R⁸ independently of one another are
selected from

25 H; F; Cl; Br; I; CN; NO₂; and C₁-C₁₀-alkyl, C₂-C₁₀-
alkenyl or C₂-C₁₀-alkynyl, each of which is branched or
unbranched and monosubstituted or polysubstituted or
unsubstituted;

30 OR¹⁴, C(O)R¹⁴, C(O)OR¹⁴ or SR¹⁴, R¹⁴ being selected from

H; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl,
each of which is branched or unbranched and
monosubstituted or polysubstituted or

35 unsubstituted; C₃-C₈-cycloalkyl which is saturated
or unsaturated and monosubstituted or

polysubstituted or unsubstituted, or a corresponding heterocycle in which at least one ring C atom is replaced by S, O or N; alkylaryl or alkylheteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and aryl or heteroaryl, each of which is monosubstituted or polysubstituted or unsubstituted; and

5

10 NR¹⁵R¹⁶ or NR¹⁵C(O)R¹⁶, R¹⁵ and R¹⁶ independently of one another being selected from

15 H; O; C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl or C₂-C₁₀-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted.

10. Salts according to one of Claims 1 to 9, characterized in that R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

20

25 H; F; Cl; Br; I; CN; NO₂; and C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl, each of which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted;

OR¹⁴, C(O)R¹⁴, C(O)OR¹⁴ or SR¹⁴, R¹⁴ being selected from

30 H; C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

35 preferably, R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

H; F; Cl; Br; I; CN; and C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted;

5 OR¹⁴ or SR¹⁴, R¹⁴ being selected from C₁-C₄-alkyl which is branched or unbranched and monosubstituted or polysubstituted or unsubstituted; and aryl which is monosubstituted or polysubstituted or unsubstituted;

10 in particular, R⁵, R⁶, R⁷ and R⁸ independently of one another are selected from

15 H; F; Cl; Br; I; CN; CH₃; CF₃; t-butyl; i-butyl; -OCH₃; -OCF₃; -SCH₃ and -O-phenyl.

11. Salts according to one of Claims 1 to 10, characterized in that

20 R⁵, R⁶ and R⁸ are H and R⁷ is Cl, or R⁵ and R⁷ are H and R⁶ and R⁸ are Cl.

25 12. Salts of substituted 1,2,3,4-tetrahydroquinoline-2-carboxylic acid derivatives according to one of Claims 1 to 11, characterized in that they are salts of the following compounds:

30 7,9-dichloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]-quinoline-4-carboxylic acid,

8-chloro-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-carboxylic acid,

35 6-chloro-7-trifluoromethyl-4-(2,4,6-trimethylphenyl)-

1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(2-hydroxyethoxy)-6-trifluoromethoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

6-iodo-4-(4-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

5,7-dichloro-4-phenyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-

10 carboxylic acid,

5,7-dichloro-4-p-tolyl-1,2,3,4-tetrahydroquinoline-2-

carboxylic acid,

15 5,7-dichloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(2-fluorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

20

5,7-dichloro-4-(3-fluorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(4-fluorophenyl)-1,2,3,4-

25 tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(2-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

30 5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(3-bromophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

35

5,7-dichloro-4-(4-bromophenyl)-1,2,3,4-tetrahydroquinoline-

2-carboxylic acid,

7,8-dichloro-4-(2-chlorophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

6-cyano-4-(2,3,4-trimethoxyphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

6,8,9-trichloro-2,3,3a,4,5,9b-hexahydrofuro[3,2-c]-

10 quinoline-4-carboxylic acid,

8-methoxy-4-(4-methoxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

15 5,6,8-trichloro-4-(4-hydroxyphenyl)-3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(3,4-dimethoxyphenyl)-8-ido-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

20

6-ido-4-(4-methylsulfanylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(4-ethoxy-3-methoxyphenyl)-6-phenoxy-1,2,3,4-

25 tetrahydroquinoline-2-carboxylic acid,

4-(2-ethoxynaphthalen-1-yl)-6-ido-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

30 8-chloro-4-(4-propoxyphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

4-(2,4-dimethoxy-3-methylphenyl)-6-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

35

4-anthracen-9-yl-6-chloro-8-methyl-1,2,3,4-

tetrahydroquinoline-2-carboxylic acid,

6-sec-butyl-4-naphthalen-1-yl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

4-(4-hydroxyphenyl)-3-methyl-8-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

8-chloro-6-fluoro-4-naphthalen-2-yl-1,2,3,4-

10 tetrahydroquinoline-2-carboxylic acid,

4-(4-methoxyphenyl)-3-methyl-6-phenoxy-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

15 6-chloro-8-fluoro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

8-chloro-6-fluoro-4-m-tolyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

20

4-(4-bromophenyl)-6-chloro-8-fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

7,8-dichloro-4-(2,4-dimethylphenyl)-1,2,3,4-

25 tetrahydroquinoline-2-carboxylic acid,

6-chloro-4-(4-chlorophenyl)-7-trifluoromethyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

30 4-(2-chlorophenyl)-6-cyano-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

6-bromo-8-chloro-4-(2,4-dimethylphenyl)-1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

35

6-bromo-4-(2-bromophenyl)-8-chloro-1,2,3,4-

tetrahydroquinoline-2-carboxylic acid,

4-(4-hydroxy-3-methoxyphenyl)-3-methyl-6-methylsulfanyl-
1,2,3,4-tetrahydroquinoline-2-carboxylic acid,

5

6-cyano-3,4-bis(4-methoxyphenyl)-1,2,3,4-
tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-

10 tetrahydroquinoline-2-carboxylic acid,

5,7-dichloro-4-(3-chlorophenyl)-1,2,3,4-

tetrahydroquinoline-2-carboxylic acid,

15 5,7-dichloro-4-(4-chlorophenyl)-1,2,3,4-
tetrahydroquinoline-2-carboxylic acid,

1,3-dichloro-5,6,6a,7,8,12b-hexahydrobenzo[k]-
phenanthridine-6-carboxylic acid,

20

1,3-dichloro-5,6a,7,11b-tetrahydro-6H-indeno[2,1-c]-
quinoline-6-carboxylic acid,

5,7-dichloro-4-(3,5-dimethylphenyl)-1,2,3,4-

25 tetrahydroquinoline-2-carboxylic acid and

7,9-dichloro-2,3,3a,4,5,9b-hexahydro-1H-cyclopenta[c]-
quinoline-4-carboxylic acid,

30

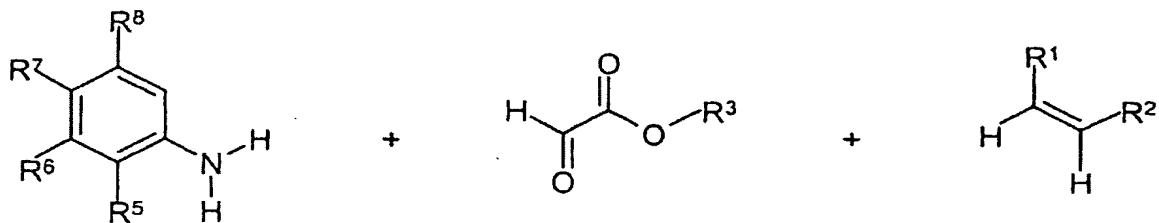
preference being given to sodium 7,9-dichloro-
3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinoline-4-
carboxylate or sodium 7,9-dichloro-2,3,3a,4,5,9b-
hexahydro-1H-cyclopenta[c]quinoline-4-carboxylate,
especially sodium 7,9-dichloro-3a,4,5,9b-tetrahydro-
3H-cyclopenta[c]quinoline-4-carboxylate.

35

13. Salts according to one of Claims 1 to 12 in the form of the alkali metal salts, preferably the sodium or potassium salts and especially the sodium salts.

5 14. Process for the preparation of salts according to Claim 1 in which $R^4 = H$, characterized in that anilines of formula II, in which R^5 , R^6 , R^7 and R^8 each independently of one another have one of the meanings indicated in Claim 1 or are provided with a protecting group,

10



II

III

IV

15 glyoxalic acid esters or optionally glyoxalic acid of formula III and olefins of formula IV, in which R^1 , R^2 and R^3 each independently of one another have one of the meanings indicated in Claim 1 or are provided with a protecting group, are reacted with trifluoroacetic acid at between 0°C and 100°C, any ester groups existing when this basic process has ended being saponified and/or the product 20 formed in the basic process optionally being brought into contact with a strong base, which may already contain the desired cation, in order to form a salt.

25 15. Process according to Claim 14, characterized in that the reaction time is 0.25 - 12 hours, preferably at most 2 h, the reaction is carried out preferably at a temperature of between 20 and 40°C and particularly preferably at room temperature, and/or the reaction is a one-pot reaction.

16. Process for the preparation of salts according to
Claim 1 in which $R^4 \neq H$, characterized in that, when the
reaction according to Claim 14 has ended, the reaction
5 product in which $R^4 = H$ is reacted in a consecutive reaction
in known manner so that the hydrogen is substituted by R^4
having the other meanings of R^4 in Claim 1.

17. Process according to one of Claims 14 to 16,
10 characterized in that, in a starting material used in the
processes, at least one OH group has been replaced by an
 $OSi(Ph)_2$ tert-butyl group, at least one SH group has been
replaced by an S-p-methoxybenzyl group and/or at least one
NH₂ group has been replaced by an NO₂ group, and at least
15 one and preferably all of the $OSi(Ph)_2$ tert-butyl groups are
cleaved with tetrabutylammonium fluoride in
tetrahydrofuran, and/or at least one and preferably all of
the p-methoxybenzyl groups are cleaved with a metal amide,
preferably sodamide, and/or at least one and preferably all
20 of the NO₂ groups are preferably all reduced to NH₂ before
the end product is purified.

18. Process according to one of Claims 14 to 17,
characterized in that, before the end product is purified,
25 a product of the process having at least one C(O)OCH₃ and/or
C(S)OCH₃ group, or a product of the process in which $R^3 =$
C₁₋₄-alkyl, especially a product of the process in which $R^3 =$
CH₃ or C₂H₅, is saponified with KOH solution or NaOH
solution in methanol or ethanol at 0°C - 100°C, preferably
30 at 40°C - 60°C.

19. Drug containing, as the active ingredient, at least
one salt according to one of Claims 1 to 13, optionally in
the form of its racemates or its pure stereoisomers,
35 especially enantiomers or diastereoisomers, or in the form
of mixtures of the stereoisomers, especially the

enantiomers or diastereoisomers, in any desired mixing ratio, and optionally containing suitable additives and/or auxiliary substances and/or optionally other active ingredients.

5

20. Use of at least one salt according to one of Claims 1 to 13, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially 10 the enantiomers or diastereoisomers, in any desired mixing ratio, for the preparation of a drug for the treatment of pain, especially neuropathic and/or chronic pain, and/or for the treatment of migraine.

15 21. Use of at least one salt according to one of Claims 1 to 13, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially 20 the enantiomers or diastereoisomers, in any desired mixing ratio, for the preparation of a drug for the treatment of urinary incontinence, pruritus, tinnitus aurium and/or diarrhoea.

25 22. Use of at least one salt according to one of Claims 1 to 13, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially 30 the enantiomers or diastereoisomers, in any desired mixing ratio, for the preparation of a drug for the treatment/ prophylaxis of epilepsy, Parkinson's disease, Huntington's chorea, glaucoma, osteoporosis, ototoxicity, withdrawal symptoms associated with alcohol and/or drug abuse, stroke, cerebral ischaemia, cerebral infarction, cerebral oedema, hypoxia and anoxia, and/or for anxiolysis and/or 35 anaesthesia.

23. Use of at least one salt according to one of Claims 1 to 13, optionally in the form of its racemates or its pure stereoisomers, especially enantiomers or diastereoisomers, or in the form of mixtures of the stereoisomers, especially 5 the enantiomers or diastereoisomers, in any desired mixing ratio, for the preparation of a drug for the treatment/prophylaxis of schizophrenia, Alzheimer's disease, psychosis due to a raised amino acid level, AIDS-related dementia, encephalomyelitis, Tourette syndrome, 10 perinatal asphyxia, inflammatory and allergic reactions, depression, drug and/or alcohol abuse, gastritis, diabetes, cardiovascular disease, respiratory tract disease, cough and/or mental disease.